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THE
COLLECTED PAPERS
OF
SYDNEY RINGER,

M.D., F.R.C.P., F.R.S.

VOL. I.—PAPERS CONTRIBUTED TO THE "JOURNAL OF PHYSIOLOGY."

VOL. II.—PAPERS CONTRIBUTED TO "THE PRACTITIONER."

VOL. III.—CONTRIBUTIONS TO VARIOUS JOURNALS.

ALSO

A LIST OF THE PAPERS AND REFERENCES CONTAINED IN
"THE LANCET," AND "BRITISH MEDICAL JOURNAL,"

AND

AN APPRECIATION OF DR. RINGER,
BY BENJAMIN MOORE, M.A., D.Sc., M.R.C.S., L.R.C.P.

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CONTENTS.

VOLUME I.

	PAGE
In Memory of Sydney Ringer, 1835-1910. By Benjamin Moore	1
Concerning the Effects on Frogs of Arrest of the Circulation, and an Explanation of the Action of Potash Salts on the Animal Body. By Ringer and Murrell	22
The Action of Arseniate of Soda and Arsenious Acid on Frogs. By Ringer and Murrell	47
Concerning the Action of Aconitia on the Nervous and Muscular System of Frogs. By Ringer and Murrell	66
The Action of Tartar Emetic, Hydrocyanic Acid and Veratria on the Animal Body. By Ringer and Murrell	75
On Pituri. By Ringer and Murrell	81
A Few Further Experiments with Pituria. By Ringer and Murrell.	90
On the Antagonism between Pilocarpine and Extract of Amanita Muscaria. By Ringer and Murrell	93
On the Physiological Action of Narcissia, an Alkaloid, obtained from the Bulb of the common Daffodil (<i>Narcissus Pseudo-Narcissus</i>). By Ringer and Morshead	103
On the Physiological Action of the common Snowdrop (<i>Galanthus Nivalis</i>) and of the Jonquil. By Ringer and Morshead	123
On the Relative Paralysing Action of Atropia and Pilocarpine on the Heart. By Ringer and Morshead	127
Concerning the Action of Common Salt, Sulphate of Atropia, Bromide of Conia and Sulphate of Nicotine on Muscular Irritability. By Ringer and Morshead	144
On the Antagonisms of Aconitia on the Frog's Heart	154
Concerning the Influence of Season and of Temperature on the Action and on the Antagonisms of Drugs	161
Regarding the Action of Hydrate of Soda, Hydrate of Ammonia, and Hydrate of Potash on the Ventricle of the Frog's Heart	171
Concerning the Influence exerted by each of the Constituents of the Blood on the Contraction of the Ventricle	179

	PAGE
A Further Contribution Regarding the Influence of the Different Constituents of the Blood on the Contraction of the Heart	193
A Third Contribution Regarding the Influence of the Inorganic Constituents of the Blood on the Ventricular Contraction	207
Of the Influence of certain Drugs on the Period of Diminished Excitability. By Ringer and Sainsbury	212
An Investigation Regarding the Action of Rubidium and CÆSIUM Salts compared with the Action of Potassium Salts on the Ventricle of the Frog's Heart	228
Concerning the Influence of Saline Media on Fish, etc.	240
On the Mutual Antagonism between Lime and Potash Salts, in Toxic Doses	259
An Experimental Investigation showing that Veratria is similar to Lime Salts, in many respects, as regards their Action on the Ventricle, also showing that Veratria and Potash Salts are reciprocally Antagonistic	267
Concerning the Action of Small Quantities of Calcium, Sodium, and Potassium Salts upon the Vitality and Function of Contractile Tissue and the Cuticular Cells of Fishes. By Ringer and Buxton	275
An Experimental Investigation to ascertain the Action of Veratria on a Cardiac Contraction	283
Regarding the Influence of the Organic Constituents of the Blood on the Contractility of the Ventricle	287
A Further Contribution regarding the Effect of Minute Quantities of Inorganic Salts on Organised Structures	310
Further Experiments regarding the Influence of Small Quantities of Lime, Potassium and other Salts on Muscular Tissue	321
Regarding the Action of Lime, Potassium and Sodium Salts on Skeletal Muscle	340
Concerning Experiments to Test the Influence of Lime, Sodium and Potassium Salts on the Development of Ova and Growth of Tadpoles	345
Concerning the Action of Calcium, Potassium and Sodium Salts upon the Eel's Heart and upon the Skeletal Muscles of the Frog. By Ringer and Buxton	351
Upon the Similarity and Dissimilarity of the Behaviour of Cardiac and Skeletal Muscle when brought into relation with Solutions containing Sodium, Calcium and Potassium Salts. By Ringer and Buxton	357

	PAGE
Regarding the Action of Lime Salts on Caseine and on Milk . . .	366
Further Observations on the Behaviour of Caseinogen	382
The Influence of Calcium Chloride on Egg Albumen and some of its Derivatives	390
The Influence of certain Salts upon the act of Clotting. By Ringer and Sainsbury	403
The Action of Salts upon Heat Coagulation. By Ringer and Sainsbury	420
Further Observations on the Influence of Calcium Salts in Promoting Heat Coagulation of Albumens	436
The Influence of Carbonic Acid dissolved in Saline Solutions on the Ventricle of the Frog's Heart	445
The Action of Potassium, Sodium and Calcium Salts on Tubifex Rivulorum. By Ringer and Sainsbury	451
The Influence of Saline Media on the Tadpole. By Ringer and Phear	461
The Influence of Saline Media on Tubifex Rivulorum. By Ringer and Phear	471
Further Observations regarding the Antagonism between Calcium Salts and Sodium, Potassium and Ammonium Salts	477
The Action of Distilled Water on Tubifex	483
List of Papers and References in <i>The Lancet</i>	485
List of Papers and References in <i>The British Medical Journal</i> . . .	489

CONTENTS.

VOLUME II.

	PAGE
On the Employment of Glycerine of Tannin	1
On the Employment of Digitalis in Diseases of the Heart	6
Purpuric Spots Produced by Iodides of Potassium and Iodide of Ammonium but not by Iodide of Sodium	19
On the Influence of Belladonna on Sweating	21
A Curious Case of Facial Neuralgia with Unilateral Sweating Cured by the application of Aconite Liniment	26
Some Additional Observations on the Action of Atropia on Sweating	30
A Case of Rheumatic Fever with High Temperature successfully Treated with Cold Baths	32
A Case of Rheumatic Fever Treated with a Cold Bath ; Death occurring immediately on leaving the Bath	39
Notes of Five Cases of Paracentesis Thoracis	42
A Successful Case of Traumatic Tetanus Treated by Large Doses of Calabar Bean	51
The Effects of Pilocarpine on Two Cases of Unilateral Sweating	61
A Case of Acute Mania Treated with Large Doses of Hyoscyamia, Daturine, Atropia and Ethyl-Atropia. By Ringer and Bury	67
Notes on a Case of Athetosis, preceded by Hemiplegia and Hemi-anaesthesia, and accompanied by Unilateral Sweating	71
Notes of a Post-Mortem Examination on a Case of Athetosis	91
On the Relative Action of Duboisia and Atropia	107
On the Physiological Action of an Alkaloid Extracted from the Garden Tulip—Natural Order Liliaceæ	111
On the Action of Extract of Muscaria, of Nitrate of Pilocarpine, and of Extract of Jaborandi on the Ventricle of the Frog's Heart and on the Antagonising Action of Atropia	115
Influence of Anæsthetics on the Frog's Heart	124

	PAGE
Concerning the Action of Chloride of Sodium, Chloride of Ammonium, Chloride of Potassium, Bromide of Sodium, Bromide of Ammonium, Bromide of Potassium, on the Ventricle of the Frog's Heart	143
On the Individuality of Action of the Component Parts of a Drug. By Ringer and Sainsbury	157
On the Antagonism between Veratria and Potassium Salts . . .	171
Observations on the Relative Effects of Certain Members of the Ethylic Alcohol Series on the Ventricle of the Frog's Heart. By Ringer and Sainsbury	175
An Investigation regarding the Action of Strontium and Barium Salts compared with the Action of Lime on the Ventricle of the Frog's Heart. By Ringer and Sainsbury	188
An Experimental Investigation to ascertain in what manner Soluble Oxalates Arrest Function and some Remarks on the Action of Poisons and their Antidotes	202
List of Papers and References in <i>The Lancet</i>	211
List of Papers and References in <i>The British Medical Journal</i> . .	215



CONTENTS.

VOLUME III.

Medico-Chirurgical Transactions.

	PAGE
On the Connexion Between the Heat of the Body and the Excreted amounts of Urea, Chloride of Sodium, and Urinary Water during a Fit of Ague	1

Proceedings of the Royal Society.

On the Alteration of the Pitch of Sound by Conduction through Different Media	42
---	----

Medico-Chirurgical Transactions.

On the Relative Amounts of Sugar and Urea in the Urine in Diabetes Mellitus	47
On the Temperature, Urea, Chloride of Sodium and Urinary Water in Scarlet Fever, and on a Cycle in Disease and Health . . .	77
Observations on Box (<i>Buxus Sempervirens</i>) with especial Reference to the True Nature of Tetanus. By Ringer and Murrell . . .	133

Proceedings of the Royal Society.

On the Temperature of the Human Body in Health. By Ringer and Stuart	165
--	-----

Journal of Anatomy and Physiology.

On the Effects of Sulphate of Atropia on the Nervous System of Frogs. By Ringer and Murrell	191
Further Observations and Experiments regarding the True Nature of Tetanus. By Ringer and Murrell	203
The Influence of Salicine on the Healthy Body, with Special Reference to its influence on the Temperature. By Ringer and Bury	215
Concerning the Action of Chloride of Potassium on the Nervous System of Frogs. By Ringer and Murrell	232
The Influence on the Afferent Nerves of the Frog's Leg from the Local Application of the Chlorides, Bromides and Iodides of Potassium, Ammonium and Sodium. By Ringer and Morshead . . .	236
On the Effect of the Chlorides, Bromides and Iodides of Potassium and Sodium on Frogs. By Ringer and Morshead	251

Archives of Medicine.

	PAGE
On the Physiological Action of the Bulb of the Buphane Toxicaria or Hemanthus Toxicarius Amaryllidaceæ. By Ringer and Morshead	263
The Action of Veratria on the Ventricle of the Frog's Heart . . .	283

Medico-Chirurgical Transactions.

Concerning the Action of Salts of Potash, Soda and Ammonia on the Frog's Heart. By Ringer and Sainsbury	293
Investigations into the Action of the Digitalis Group. By Ringer and Sainsbury	327
List of Papers and References in <i>The Lancet</i>	351
List of Papers and References in <i>The British Medical Journal</i> . . .	355

ON THE CONNEXION
BETWEEN THE
HEAT OF THE BODY
AND THE
EXCRETED AMOUNTS OF UREA, CHLORIDE OF
SODIUM, AND URINARY WATER,
DURING A FIT OF AGUE.¹

BY
SYDNEY RINGER, M.R.C.S.,
LATE PHYSICIAN'S ASSISTANT IN UNIVERSITY COLLEGE HOSPITAL.

COMMUNICATED BY
RICHARD QUAIN, F.R.S.

Received June 6th—Read June 28th, 1859.

THE observations on the temperature of the body during ague fits are now numerous and accordant,² and may be considered sufficient to indicate the general condition of the animal heat during the several stages of ague.

¹ The following observations were made at the suggestion of Dr. Parkes, from whom, from time to time, I have received assistance. Dr. Parkes has also supplied the entire literature in the paper, and has kindly examined it with care.

² Zimmermann; Bärensprung, Müller's 'Archiv,' 1852, p. 217; Michael, 'Archiv für Phys. Heilk.,' 1856, p. 39; Wunderlich, 'Archiv für Phys. Heilk.,' 1858, p. 12.

The increase in the amount of urea and of chloride of sodium during the cold and hot stages has been affirmed by Traube and Jochmann,¹ Moos,² Redenbacher,³ and Hammond.⁴ These observations have been criticised, however, and certainly some of the cases were not examined with any great minuteness. In no case yet reported either has any comparison been drawn between the rise in the temperature and the amount of the urea and chloride of sodium.⁵ It therefore seemed extremely desirable, on the occasion of a patient with ague being admitted into University College Hospital, under the care of Dr. Parkes, to examine the subject, and to see, first of all, whether the increase of urea and of chloride of sodium really occur in the cold and hot stages of ague, as affirmed by Traube, Redenbacher, and Hammond; and, secondly, whether any close connexion could be traced between the amount of urea and the abnormal temperature. My position as one of the resident officers in the hospital at the time gave me the opportunity of carrying out the inquiry with all the minuteness necessary for accuracy.

The general results may be thus stated—that not only was the increase of urea and of chloride of sodium constant during the cold and hot stages of ague, but that their amount was in very close relation to the temperature. The first case recorded in this paper will, I believe, give little short of mathematical proof of the connexion between these two phenomena, viz., the increase of heat of body and of the excretion of urea and chloride of sodium.

The second case communicated is one in which the phenomena were less carefully observed, but it is valuable as affording another instance of the increase of urea and chloride of sodium during the fit.

¹ 'Deutsche Klinik,' No. 46, Nov., 1855.

² Henle's 'Zeitschrift für rat. Med.,' Band vii, p. 291.

³ Henle's 'Zeitschrift,' Band ii (Dritte Reihe), p. 384.

⁴ 'American Journal of Med. Science,' April, 1858.

⁵ Some other observations have been made on the excretions of twenty-four hours, but these are of little value as febrile and non-febrile bones are put together.

In addition, a case of hectic fever occurring in phthisis has been narrated, for in this case the phenomena were found to be identical with those presented by malarial ague. The result was the same in both cases, although the causes were so different.

CASE 1. *Quotidian ague*.—The patient, a man, was first attacked by tertian in August last, whilst working at Maldon, in Essex. The ague continued on him for three weeks, by which time he was apparently cured; he remained working at the same place till the December following. At that time, moving up to London, he broke his leg, and was carried to Charing Cross Hospital. Upon being discharged from that institution, cured, he caught cold, and an attack of ague immediately followed, and has continued more or less since, being immediately brought on by exposure to cold. This long continuance produced the usual effects of prolonged ague; and in this state he was admitted into the hospital, the disease having changed a day or two previously from the tertian to the quotidian type.

He suffers from slight aortic obstructive disease. His pulse is continually about 120 per minute,¹ exceedingly irregular in both force and rhythm. His arteries are very tortuous and visible. He never suffered from rheumatism, and has no arcus senilis. Except the above heart-disease, he suffers from no organic lesion.

He is fifty-nine years of age, but looks much older. His weight is 144 pounds; his height five feet nine and three quarter inches. His vital capacity (Hutchinson's spirometer) is 140 cubic inches.

The examination was conducted in the following manner. The patient was put to bed, and his urine collected through the night. At 5 a.m. he had breakfast, consisting of two eggs, bread and butter, and tea, the latter being measured. At 6 a.m. he was made to pass his urine, and all passed at

¹ No tables are therefore given of the pulse.

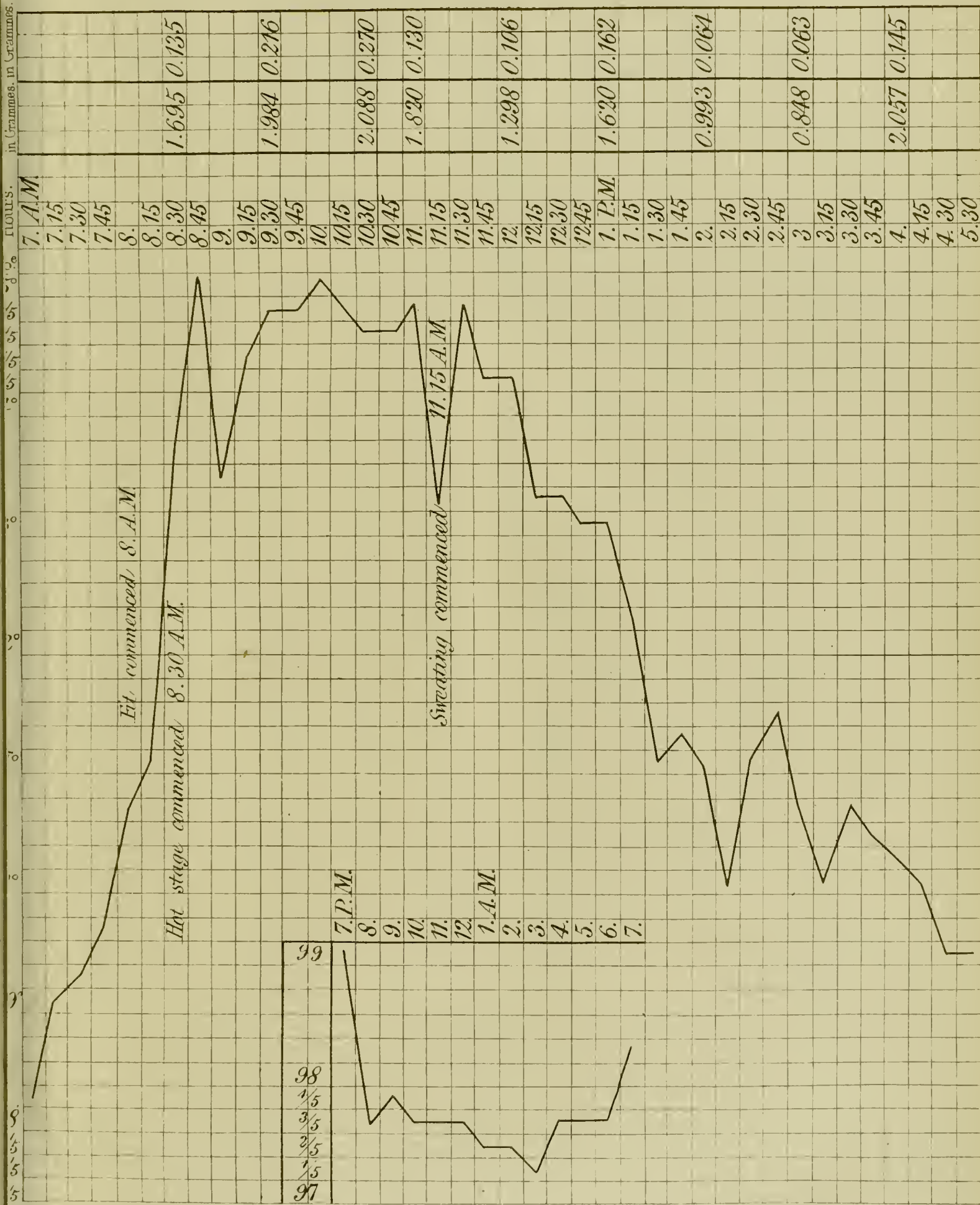
the time was mixed with that passed during the night. The thermometer (a good one, by Negretti and Zambra, and divided into fifths of a Fahrenheit degree) was next placed in his axilla, and kept there during the remainder of the day, the temperature being noted down every quarter of an hour. He was also made to pass his urine hourly, or upon the commencement of another stage, before the completion of the hour, and the next hour was dated from that time; by this means we not only obtained the urine of every hour, but also of each stage, separately. The patient was allowed no food until the completion of the fit, when he had a good meat dinner and six ounces of wine. Lemonade he was permitted to drink *ad libitum*, but the quantity was always measured and noted, with the time at which it was taken. He was weighed immediately after his breakfast, and again at the termination of the fit, and during this time no motions were allowed to be passed. The patient was purposely kept without medicine. In determining the amount of urea and chloride of sodium, Liebig's volumetric method with nitrate of mercury was used.

It was not possible to determine the other urinary constituents in this case. The chloride of sodium was not got rid of before testing for urea, but the usual correction was made.

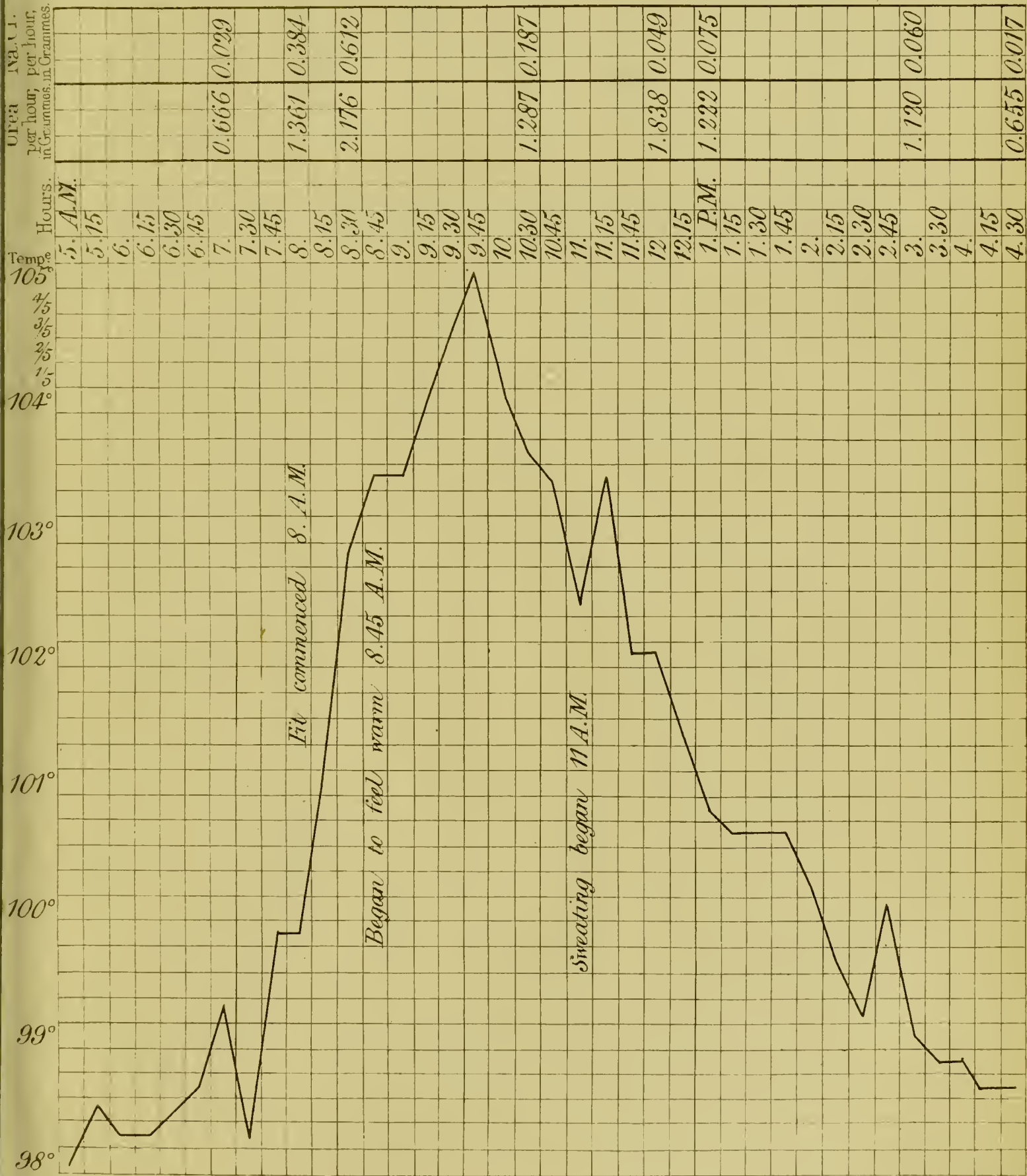
The following charts show the variations in the temperature in fifths of a degree, as taken every quarter of an hour. Above the table are two columns, one showing the amount of urea, the other the amount of chloride of sodium, poured out. The quantity per hour is stated in each case, and put down in the column denoting the time at which it was passed. It indicates, of course, the quantity formed during the previous hour. The amounts of urea and chloride of sodium are given always in French grammes, and the water in cubic centimetres. The commencement of each stage, as judged of in the usual way, by the sensations of the patient, is also noted in the column proper to the time at which it began.

For the purpose of greater clearness and of giving fuller

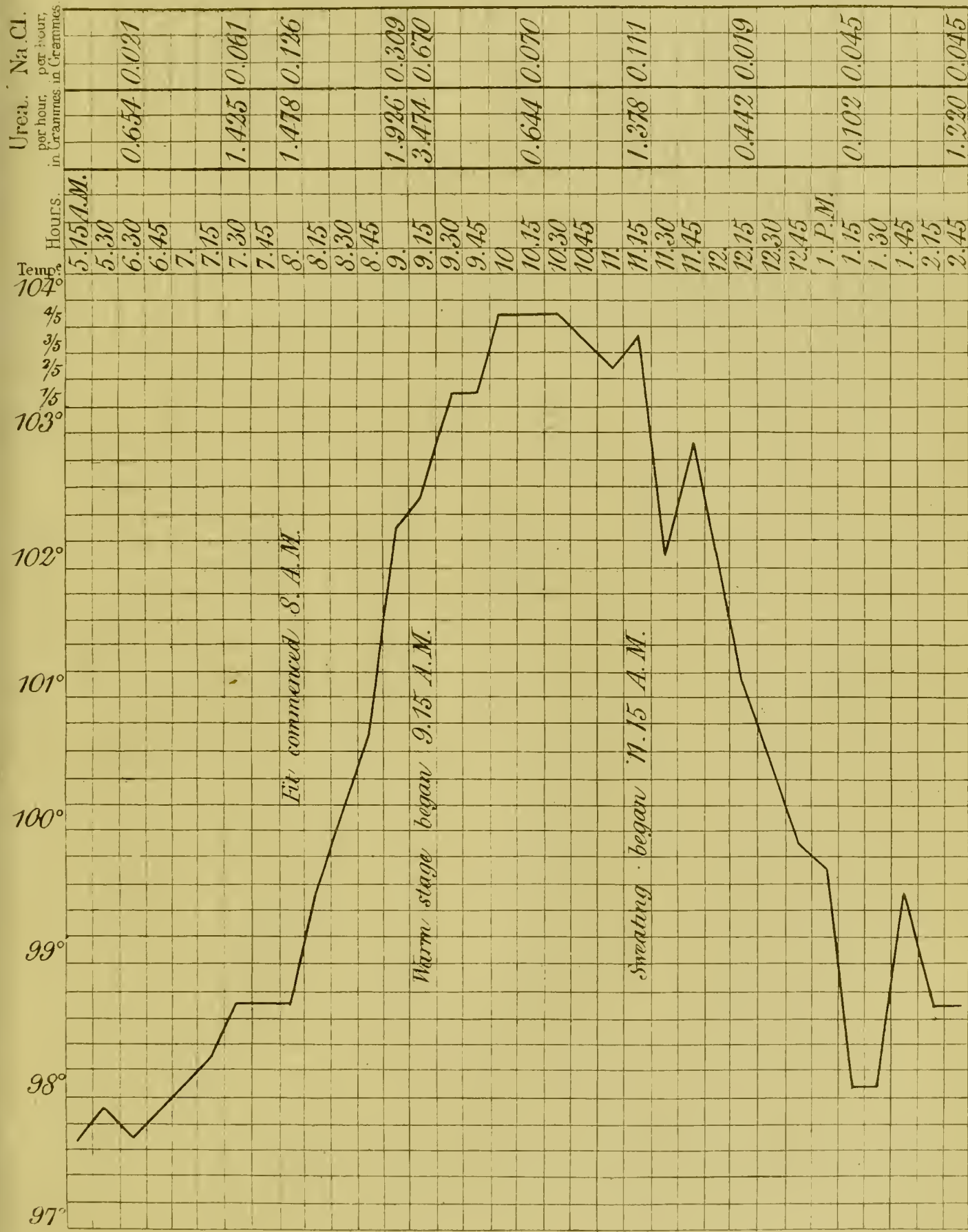
APRIL 6TH



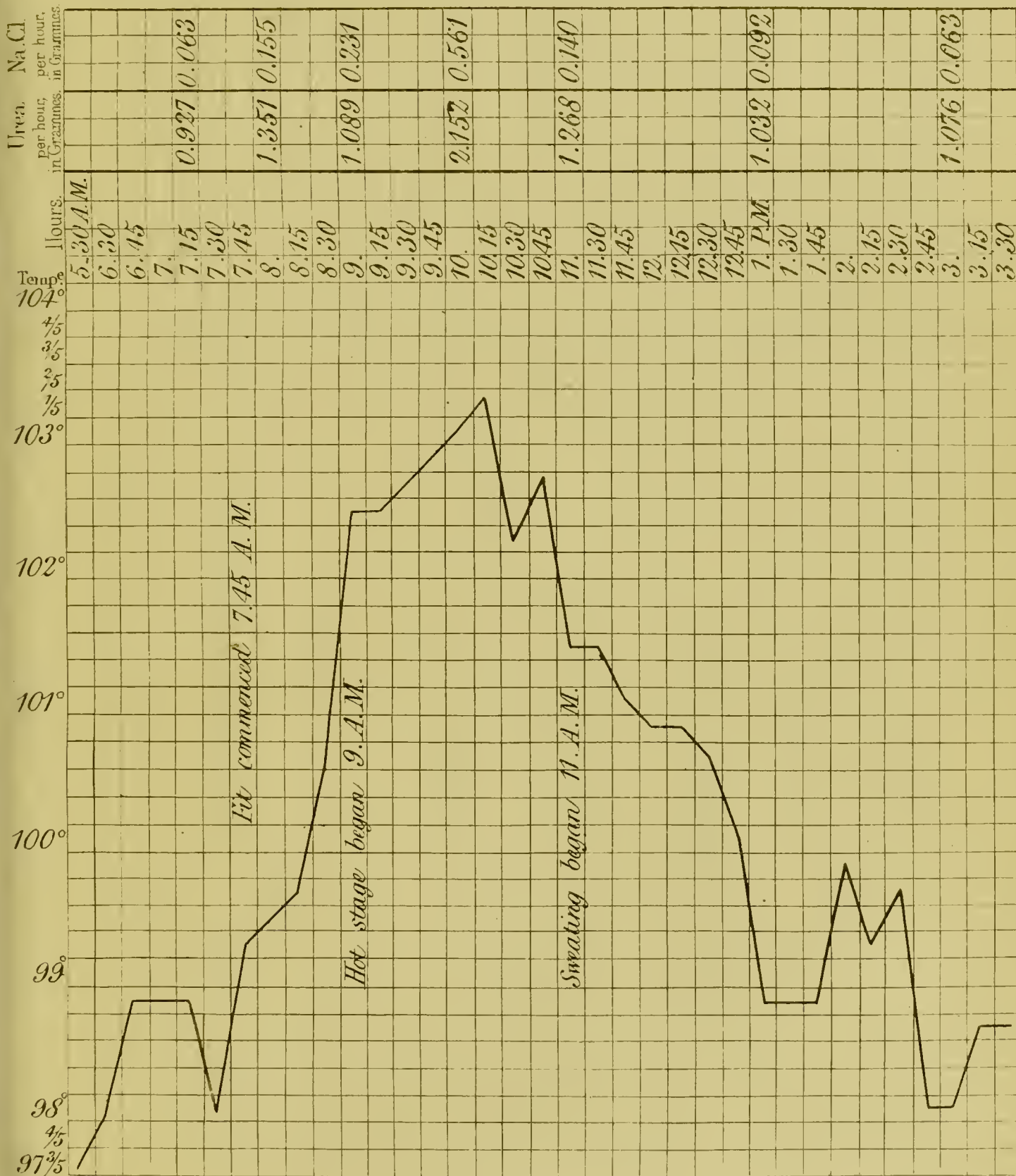
APRIL 7TH



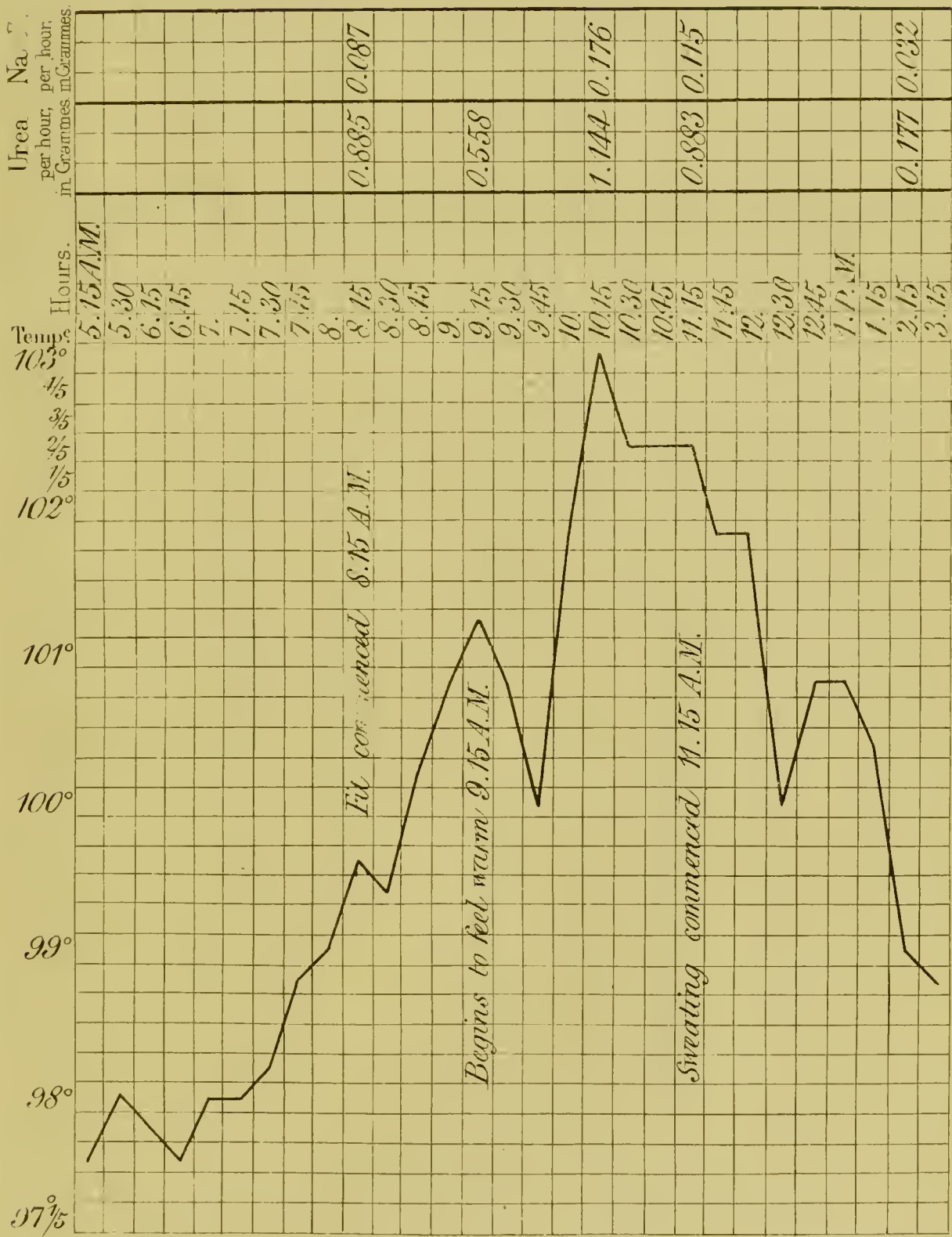
APRIL 8TH



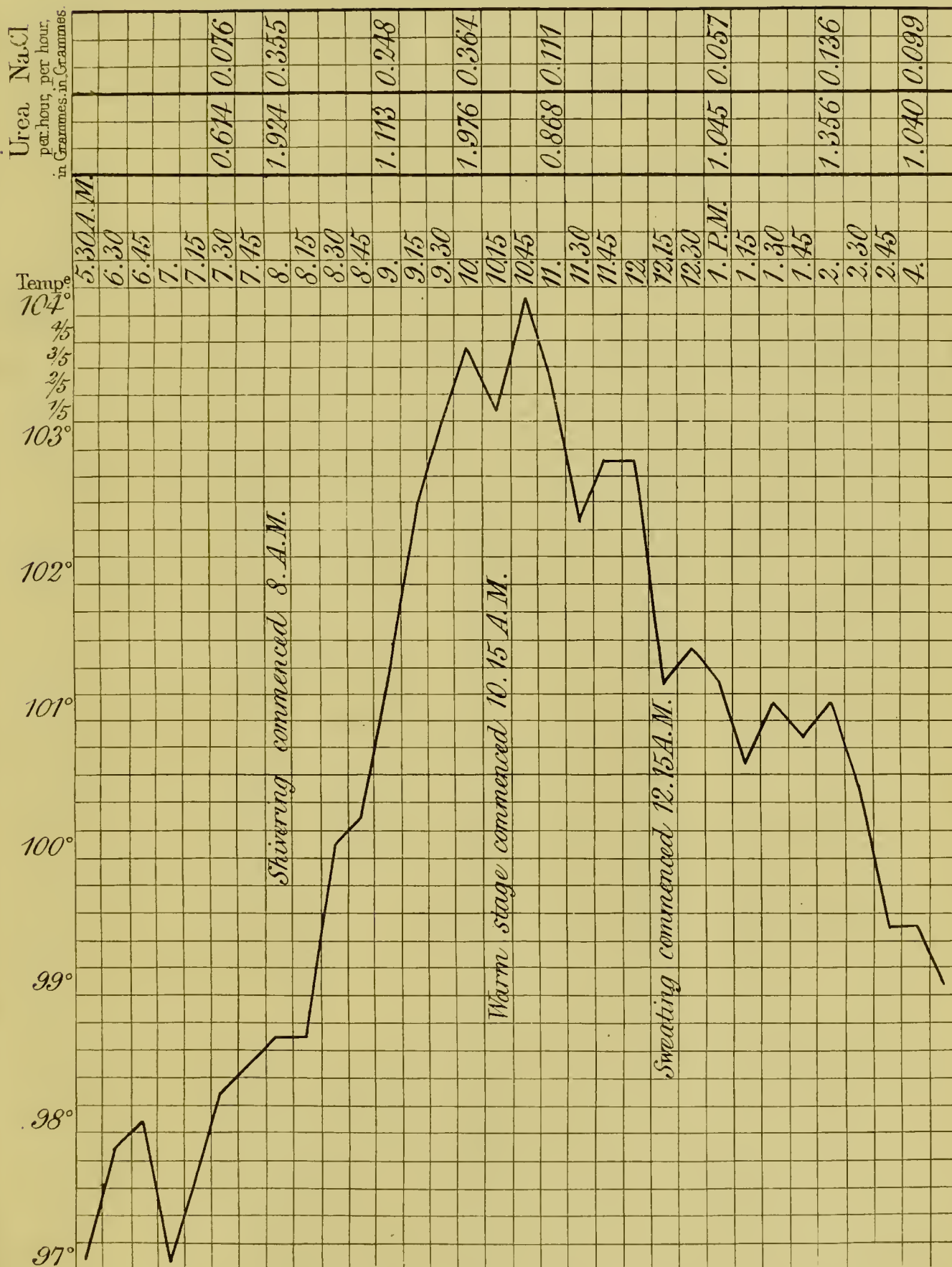
APRIL 9TH



APRIL 10TH



APRIL 11TH



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details, tables are added, recapitulating the amount of the urea, chloride of sodium, and water, separately. In the first column of each table the stages are written down; in the next the hour at which the urine was passed; then follows the total amount of urea contained in the urine passed during the specified time; the next column shows the amount reduced to hours; and, lastly, the average amount of each stage per hour is given.

TABLE.
APRIL 6th.—UREA.

Stage.	Hour.	Total Quantity in this time.	Quantity per hour.	Average Quantity per hour during period.
		Grammes.	Grammes.	Grammes.
Cold	7.45 to 8.30 a.m.	1.356	1.695	1.695
Hot	8.30 to 9.30 a.m.	1.984	1.984	} 1.964
	9.30 to 10.30 a.m.	2.088	2.088	
	10.30 to 11 a.m.	0.910	1.820	
Sweating	11 to 12 a.m.	1.289	1.289	} 1.363
	12 to 1 p.m.	1.620	1.620	
	1 to 2 p.m.	0.993	0.993	
	2 to 3 p.m.	0.848	0.848	
	3 to 4 p.m.	2.057	2.057	

CHLORIDE OF SODIUM.

Cold	7.45 to 8.30 a.m.	0.108	0.135	0.135
Hot	8.30 to 9.30 a.m.	0.216	0.216	} 0.220
	9.30 to 10.30 a.m.	0.270	0.270	
	10.30 to 11 a.m.	0.065	0.130	
Sweating	11 to 12 a.m.	0.106	0.106	} 0.108
	12 to 1 p.m.	0.162	0.162	
	1 to 2 p.m.	0.064	0.064	
	2 to 3 p.m.	0.063	0.063	
	3 to 4 p.m.	0.145	0.145	

WATER.

Cold	7.45 to 8.30 a.m.	75 c.c.		
	8.30 to 9.30 a.m.	80 c.c.		
Hot	9.30 to 10.30 a.m.	90 c.c.		
	10.30 to 11 a.m.	82 c.c.		
Sweating	11 to 12 a.m.	59 c.c.		
	12 to 1 p.m.	90 c.c.		
	1 to 2 p.m.	54 c.c.		
	2 to 3 p.m.	53 c.c.		
	3 to 4 p.m.	121 c.c.		

APRIL 7th.—UREA.

Stage.	Hour.	Total Quantity in this time.	Quantity per hour.	Average Quantity per hour during period.
		Grammes.	Grammes.	Grammes.
During night...	3 p.m. to 5.30 a.m.	10.272	0.684	0.684
Period immedi- ately before	5.30 to 7 a.m.	0.999	0.666	0.666
shivering	7 to 8 a.m.	1.361	1.361	1.361
Cold	8 to 8.30 a.m.	1.088	2.176	2.176
Hot	8.30 to 10.30 a.m.	2.575	1.287	1.287
Sweating	11 to 12 a.m.	0.838	0.838	} 0.935
	12 to 1 p.m.	1.222	1.222	
	1 to 3 p.m.	2.240	1.120	
	3 to 5 p.m.	1.311	0.655	

CHLORIDE OF SODIUM.

During night ...	3 p.m. to 5.30 a.m.	0.642	0.029	0.029
Period before	5.30 to 7 a.m.	0.440	0.29	0.29
shivering	7 to 8 a.m.	0.384	0.384	0.384
Cold	8 to 8.30 a.m.	0.306	0.612	0.612
Hot	8.30 to 10.30 a.m.	0.375	0.187	0.187
	11 to 12 a.m.	0.049	0.049	} 0.064
	12 to 1 p.m.	0.075	0.075	
	1 to 3 p.m.	0.120	0.060	
	3 to 5 p.m.	0.034	0.017	

QUANTITY OF URINE PASSED.

Before shivering	3 p.m. to 5.30 a.m.	36 c.c.	
	5.30 to 7 a.m.	25 c.c.	
	7 to 8 a.m.	80 c.c.	
Cold	8 to 8.30 a.m.	136 c.c.	
Hot	8.30 to 10.30 a.m.	62 c.c.	
	11 to 12 a.m.	33 c.c.	
	12 to 1 p.m.	50 c.c.	
	1 to 3 p.m.	50 c.c.	
	3 to 5 p.m.	28 c.c.	

APRIL 8th.—UREA.

Period immedi- ately before	5 p.m. to 6.30 a.m.	8.832	0.654	0.654
shivering	6.30 to 7.30 a.m.	1.425	1.425	} 1.452
	7.30 to 8 a.m.	0.738	1.478	
Cold	8 to 9 a.m.	1.926	1.926	} 2.700
	9 to 9.15 a.m.	0.868	3.474	
Hot	9.15 to 10.15 a.m.	0.644	0.644	} 1.011
	10.15 to 11.15 a.m.	1.378	1.378	
Sweating	11.15 to 12.15 p.m.	0.044	0.044	} 0.498
	12.15 to 1.15 p.m.	0.102	0.102	
	1.15 to 2.45 p.m.	1.830	1.220	

CHLORIDE OF SODIUM.

Stage.	Hour.	Total Quantity in this time.	Quantity per hour.	Average Quantity per hour during period.
		Grammes.	Grammes.	Grammes.
Night	5 p.m. to 6.30 a.m.	0.576	0.021	0.021
Before fit	6.30 to 7.30 a.m.	0.064	0.064	} 0.095
	7.30 to 8 a.m.	0.063	0.162	
Cold	8 to 9 a.m.	0.309	0.309	} 0.381
	9 to 9.15 a.m.	0.167	0.670	
Hot	9.15 to 10.15 a.m.	0.070	0.070	} 0.090
	10.15 to 11.15 a.m.	0.111	0.111	
	11.15 to 12.15 p.m.	0.019	0.019	} 0.027
	12.15 to 1.15 p.m.	0.045	0.045	
	1.15 to 2.45 p.m.	0.045	0.030	

QUANTITY OF URINE PASSED.

Night	5 p.m. to 6.30 a.m.	42 c.c.		
Before fit	6.30 to 7.30 a.m.	54 c.c.		
	7.30 to 8 a.m.	60 c.c.		
Cold	8 to 9 a.m.	86 c.c.		
	9 to 9.15 a.m.	172 c.c.		
Hot	9.15 to 10.15 a.m.	26 c.c.		
	10.15 to 11.15 a.m.	52 c.c.		
	11.15 to 12.15 p.m.	13 c.c.		
	12.15 to 1.15 p.m.	38 c.c.		
	1.15 to 2.45 p.m.	50 c.c.		

APRIL 9TH.—UREA.

Immediately be-	6.15 to 7.15 a.m.	0.927	0.927	0.927
fore shivering..	7.15 to 8 a.m.	1.081	1.351	1.351
Cold	8 to 9 a.m.	1.089	1.089	1.089
Hot	9 to 10 a.m.	2.152	2.152	} 1.710
	10 to 11 a.m.	1.268	1.268	
Sweating	11 to 1 p.m.	2.164	1.032	} 1.129
	1 to 3 p.m.	2.353	1.076	

CHLORIDE OF SODIUM.

Before fit	6.15 to 7.15 a.m.	0.063	0.063	0.063
	7.15 to 8 a.m.	0.124	0.155	0.155
Cold	8 to 9 a.m.	0.231	0.231	0.231
Hot	9 to 10 a.m.	0.561	0.561	} 0.351
	10 to 11 a.m.	0.140	0.140	
Sweating	11 to 1 p.m.	0.184	0.092	} 0.078
	1 to 3 p.m.	0.127	0.063	

QUANTITY OF URINE PASSED.

Before fit	6.15 to 7.15 a.m.	35 c.c.		
	7.15 to 8 a.m.	61 c.c.		
Cold	8 to 9 a.m.	55 c.c.		
	9 to 10 a.m.	117 c.c.		
	10 to 11 a.m.	52 c.c.		
	11 to 1 p.m.	44 c.c.		
	1 to 3 p.m.	53 c.c.		

APRIL 10TH.—UREA.

Stage.	Hour.	Total Quantity in this time.	Quantity per hour.	Average Quantity per hour during period.
		Grammes.	Grammes.	Grammes.
Before fit	6.30 to 8.15 a.m.	1.420	0.885	0.885
Cold	8.15 to 9.15 a.m.	0.558	0.558	0.558
Hot	9.15 to 10.15 a.m.	1.144	1.144	} 1.013
	10.15 to 11.15 a.m.	0.883	0.883	
Sweating	11.15 to 2.15 p.m.	0.532	0.177	0.177

CHLORIDE OF SODIUM.

Before fit	6.30 to 8.15 a.m.	0.140	0.087	0.087
	8.15 to 9.15 a.m.	Urine	lost.	
Hot	9.15 to 10.15 a.m.	0.176	0.176	} 0.145
	10.15 to 11.15 a.m.	0.115	0.115	
Sweating	11.15 to 2.15 p.m.	0.070	0.032	0.032

QUANTITY OF URINE PASSED.

Before fit	6.30 to 8.15 a.m.	50 c.c.		
Cold	8.15 to 9.15 a.m.	20 c.c.		
Hot	9.15 to 10.15 a.m.	44 c.c.		
	10.15 to 11.15 a.m.	32 c.c.		
	11.15 to 2.15 p.m.	22 c.c.		

APRIL 11TH.—UREA.

During night ...	2.15 p.m. to 6 a.m.	9.785	0.609	0.609
	6 to 7.30 a.m.	0.921	0.614	0.614
Immediately before fit ...	7.30 to 8 a.m.	0.962	1.924	1.924
Cold	8 to 9 a.m.	1.113	1.113	} 1.476
	9 to 10 a.m.	1.839	1.839	
Hot	10 to 11 a.m.	0.868	0.868	0.868
Sweating	11 to 1 p.m.	2.090	1.045	} 1.147
	1 to 2 p.m.	1.356	1.356	
	2 to 4 p.m.	2.090	1.040	

CHLORIDE OF SODIUM.

	2.15 p.m. to 6 a.m.	0.139	0.087	0.087
	6 to 7.30 a.m.	0.115	0.076	0.076
Before fit	7.30 to 8 a.m.	0.355	0.355	0.355
Cold	8 to 9 a.m.	0.248	0.248	} 0.306
	9 to 10 a.m.	0.364	0.364	
Hot	10 to 11 a.m.	0.111	0.111	0.111
Sweating	11 to 1 p.m.	0.114	0.057	} 0.097
	1 to 2 p.m.	0.136	0.136	
	2 to 4 p.m.	0.119	0.099	

QUANTITY OF URINE PASSED.

Stage.	Hour.	Total Quantity in this time.
Night	2·15 p.m. to 6 a.m.	...
	6 to 7·30 a.m.	24 c.c.
Before fit	7·30 to 8 a.m.	74 c.c.
Cold	8 to 9 a.m.	64 c.c.
	9 to 10 a.m.	76 c.c.
Hot	10 to 11 a.m.	31 c.c.
	11 to 1 p.m.	38 c.c.
	1 to 2 p.m.	57 c.c.
	2 to 4 p.m.	95 c.c.

CONCLUSIONS FROM THE PREVIOUS FACTS.

I. *Temperature.*

The temperature during the several fits, amid much general resemblance, presented numerous partial differences, all of which are, however, reducible to order.

(a) In every case, the temperature commenced to rise previous to the cold stage,¹ as experienced by the patient, that is to say, before any feeling of cold or illness of any kind. The time that it commenced, previous to the cold stage, varied from an hour and a half to three quarters of an hour, and no connexion between the time and the severity of the fit could be traced. The temperature commenced to rise—

April 6th..1½ hour before any feeling of cold or illness.

„ 7th..1 „ „

„ 8th..1½ „ „

„ 9th..1¼ „ „

„ 10th..1¼ „ „

„ 11th..¾ „ „

A close connexion between the severity of the fit and the character of the rise before the cold stage existed, the severity being in proportion to the continuousness of the rise, and also to the extent of each rise. As the fit became less severe, the temperature had a tendency either to oscillate, rise slowly, or remain stationary, and these tendencies

¹ The same fact is noted by Michael, op. cit., p. 43.

increased as the fit decreased in severity, and eventually all combined.

(*b*) During the cold stage the temperature rose throughout, the rise being greater than during any other period; but here also great variations existed, having their counterpart in variations in the severity of the fit.

Thus, in the cold stage, the temperature rises continuously when the fit is severe; then, as the severity lessens, there is a tendency for the rise at the termination of the cold stage to flag, and eventually to become stationary; then the range of each rise becomes less; and lastly, it oscillates. It also appears that the alteration first affects the commencement and termination of the cold stage, an oscillation in its middle indicating a greater diminution of the severity of the fit than at either end.

There was no connexion between the duration of the stage and the severity of the fit, as measured by the temperature. Thus, it lasted—

On the 6th	$\frac{3}{4}$ hour.
„ 7th	$\frac{3}{4}$ „
„ 8th	$1\frac{1}{4}$ „
„ 9th	$\frac{3}{4}$ „
„ 10th	1 „
„ 11th	2 hours.

The fits were most severe on the 6th and 7th, and declined in severity till the 11th, when the fit was again more severe.

(*c*) During the hot stage the temperature continued to rise, and in its early part closely corresponded to the former periods.

From a careful examination of the charts, it appears that in the severer cases the temperature in the hot stage ran up at once to its acme, and had a tendency to remain permanent; the permanency not, however, being obtained at once nor retained throughout, the temperature oscillating both at the commencement and termination. In less severe cases it ran up slowly, and did not remain stationary, and when least severe, oscillated in its rise.

The temperature in those fits becoming less severe first lost its permanency, and next the temperature rose to a less extent

and again became permanent; then, when they became still less severe, it rose to the same extent, but again lost its permanency. Again, in those cases where the temperature remained permanent, the hot stage ended at the termination of the permanent period in an oscillation, these cases being the severest at their own temperature. In all other cases the temperature fell before the sweating stage commenced, ending in an oscillation, and the less severe the fit the greater was the portion of the hot stage occupied by the fall of the temperature. Also the fit was less severe, and the fall greater, when the temperature in falling every now and then stood still for some time, and was still less severe when it oscillated.

(d) The temperature continued to fall through the sweating stage, and was often a long time before it reached the point from which it started. The temperature fell most rapidly in those cases in which the oscillations occurred, and least rapidly where the fall was continuous. Towards the termination of the sweating stage a rise occurred to a slight extent (perhaps followed by oscillations) in four of the six fits. Thus, on April 6th, sweating commenced at 11.15, when the thermometer marked $103\frac{1}{5}^{\circ}$; at 2.15 the temperature had fallen to 100° ; it then rose to 101° at 2.30, to $101\frac{2}{5}^{\circ}$ at 2.45; then fell to $100\frac{3}{5}^{\circ}$ and 100° at 3 and 3.15; then rose to $100\frac{3}{5}^{\circ}$ at 3.30, and then finally fell regularly to $97\frac{3}{5}^{\circ}$, a point not reached till seven o'clock. The charts show, at a glance, these slight but perfectly definite rises at this late period of the sweating stage.

II. Urea.

As the type of the disease in this man was quotidian, there was no opportunity of comparing the amount of urea on a fever and on a fever-free *day*. But the amount of urea passed in the fever-free *hours* was decidedly much smaller than might have been anticipated. He excreted only 0.650 grm. on an average per hour in the apyrectic period, which would give in twenty-four hours 15.600 grms., had the excretion remained at the same amount during

the whole day. Now, a man of the same weight, between twenty and forty years of age, on a good diet, as this man was, would have secreted 32 grms. in the twenty-four hours, if he passed the average amount. Our patient was, however, older (fifty-nine), and would, no doubt, form less urea than a man at a more vigorous period of life. But it can hardly be supposed that the amount would be reduced so low as $15\frac{1}{2}$ grms. in the twenty-four hours by this difference of age. It may, therefore, be concluded that, in accordance with Redenbacher's observations, the excretion of urea in the fever-free period was below the healthy amount.

The observations made by Traube, Redenbacher, and Hammond on the increase of urea during the cold and hot stages are entirely confirmed by this case, but a more minute statement of the kind and amount of the increase can now be given.

It must, however, be premised, that the only obvious causes of the increase of the urea in this case during the fit are, either the food taken at breakfast at 5 a.m., the fluid drunk during the fit, or the fit itself. No other known causes existed which could have had the effect of increasing the urea. The following objections to the idea of the food being the cause may be urged. That the amount of food was not great, and that the increase in the urea was far larger than has yet been noted after even the heaviest meal. For example, on the 7th, the amount per hour rose from 0.684 gm. to 2.176, being an increase of more than 200 per cent.; on the 8th, from 0.654 to 3.474, being an increase of nearly 500 per cent.; on the 9th and 10th, when the fits were slighter, the increase was less marked, though still considerable; while on the 11th, when the fit was severe, it was again 200 per cent. Such an amount is greater than has yet been found after an ordinary amount of food.¹ The time, however, at which the urea increases after food accords with our case; for, augmenting even

¹ Dr. Parkes has noted in one person without fever a rise from 0.665 gm. in a fasting hour to 1.554 gm. in a food hour, but this was after a hearty dinner.

during the first hour after food,¹ it attains its maximum sometimes in the third hour;² sometimes, however, not till the seventh hour; usually, however, it reaches its maximum at the fourth hour.

Now, in this case food was taken between 5 and 6 a.m., and the maximum amount of urea secreted was during the cold stage, from 8 to 9.30 a.m., or in the fourth and fifth hours. But it will probably be conceded, after it has been shown how closely the amount of the urea was associated with the variation in the temperature, that its increase in the fourth and fifth hours after food was merely a coincidence, and was not owing to the very moderate breakfast, but to the fact of the highest temperature occurring at this time. On one day, moreover, he took no food, having no appetite, and on this day the usual increase occurred. Again, after the fits were stopped by the quinine, the food was given him as usual, and the urine being collected on the same day, in the same way, comparatively little rise took place in the urea. These two last points, I conceive, set the question quite at rest.

With respect to the amount of fluid drunk, this could have no effect on the urea, as very little fluid was taken till after the time when the urea had commenced to rise. The urea, moreover, reached its maximum often at the termination of the cold stage, whilst he seldom drank anything between his breakfast and the hot stage. I believe, then, that I am justified in concluding that the rise in the amount of urea was not owing either to food or liquid. It must, therefore, have been owing to the fit.

The urea begins to increase in amount *before* the cold stage, as judged of by the first feeling of shivering, in four of the five fits. Thus, it rose—

On the 7th, from 0.666 to 1.361 per hour.

„ 8th, from 0.654 to 1.425 „

„ 9th, from 0.927 to 1.351 „

„ 11th, from 0.614 to 1.924 „

¹ Voit, quoted by Meissner, "Report on Phys. for 1857," in Henle's 'Zeitschrift,' p. 352.

² Becker, Henle's 'Zeitschrift,' 1855, p. 549.

The time it commenced to rise before the subjective fit varied. Thus—

On the 7th....	$\frac{3}{4}$ hour before.	
„ 8th....	$1\frac{1}{2}$	„
„ 9th....	$1\frac{3}{4}$	„
„ 11th....	$\frac{1}{2}$	„

It often began to increase, indeed, even before the temperature began to rise. Thus, as the temperature on the 7th rose before the fit $\frac{3}{4}$ of an hour, on the 8th $1\frac{1}{2}$, on the 9th $\frac{3}{4}$, the urea on those days commenced to rise previous to any similar change in the temperature.

Great apparent irregularity existed in the rise of urea, but a close correspondence is observed between these variations and similar ones in the temperature.

The alteration in the above case of urea and the temperature did not always exactly agree in time, though this was the rule, but sometimes the alteration in the temperature did not occur till after the alteration in the urea; the reverse never happened.

The quantity of urea continued to increase, and reached its highest point either at the termination of the cold stage, as on the 8th and 11th, or at the commencement of the hot, as on the 6th, 9th, 10th, and 12th. It then began to fall in quantity, slowly at first. On the 6th and 10th the temperature and urea commenced to fall simultaneously. On the 7th, 8th, 9th, and 11th, the temperature continued to rise, notwithstanding the fall in the urea. Up to the period when the urea commenced to decrease, the temperature rose rapidly, each rise being extensive, but after that, at the point where the urea commenced to fall, the temperature either oscillated, or every rise remained stationary for a short time, the rise being always slow and by small additions.

The urea continued to fall slowly from the end of the cold, or from the commencement of the hot stage, till the sweating stage began; and the temperature corresponding in time to the latter part of this slow decrease, after reaching its height, fell also slowly and slightly.

From the following table it appears that no close correspondence existed between the fall in the temperature towards the close of the hot stage and the decrease in the amount of urea.

Date.	Fall in Urea.	Fall in Temperature in same time.	Temperature oscillated.	Tendency to be stationary.	Temperature fell continuously.	Fall of Urea reduced to quantity for 1° Fahr.
6th	0·268	$\frac{1}{5}^{\circ}$		—		1·346
7th	0·830	$1\frac{3}{5}^{\circ}$			—	0·533
8th	1·452	$\frac{2}{5}^{\circ}$			—	...
9th	0·884	1°			—	0·884
10th	0·261	$\frac{3}{5}^{\circ}$		—		0·435
11th	1·000	$2\frac{4}{5}^{\circ}$	—			0·357

In the first column the date is given ; in the second the fall in the amount of urea, corresponding in time to the fall in the temperature, from its highest point to the commencement of the sweating stage, is given ; next, the number of degrees the temperature fell in the same time ; then, in three columns, the character of the fall is given ; and in the last column the fall in the amount of urea is reduced to the quantity corresponding to each degree. But though there is no intimate connexion, still the greater the fall in the temperature the greater is the decrease in the quantity of urea. At the same time the character of the fall varied ; thus, sometimes the temperature showed a tendency to remain stationary, then the urea fell but little, as on the 6th and 10th. On other days the temperature fell gradually, and then the fall in urea rather increased. The greatest fall occurred on those days when the temperature oscillated greatly. Thus, the least decrease in urea corresponded to that temperature which has a tendency to remain stationary, more when it fell slowly but continuously, and much the most when it oscillated, as on the 11th ; and it is

possible to judge of the rapidity of the decrease of the urea by the character of the temperature.

The temperature has been shown to fall either at the close of the hot or the commencement of the sweating stage. A similar fall occurred in the urea, and the amount of the decrease of urea corresponded to the length of the oscillation, and the subsequent rise in the urea corresponded to the rise in the oscillation, though the whole oscillation always occurred in an hour previous to that in which the subsequent rise in the urea occurred.

Date.	Fall in Temperature.	Fall in Urea.	Rise in Temperature.	Rise in Urea.
6th	$1\frac{3}{5}^{\circ}$	$\left\{ \begin{array}{c} 1.820 \\ \text{to} \\ 1.289 \end{array} \right\}$	$1\frac{3}{5}^{\circ}$	$\left\{ \begin{array}{c} 1.289 \\ \text{to} \\ 1.620 \end{array} \right\}$
7th	1°	$\left\{ \begin{array}{c} 1.287 \\ \text{to} \\ 0.838 \end{array} \right\}$	1°	$\left\{ \begin{array}{c} 0.838 \\ \text{to} \\ 1.222 \end{array} \right\}$
8th	$1\frac{3}{5}^{\circ}$	$\left\{ \begin{array}{c} 3.474 \\ \text{to} \\ 0.644 \end{array} \right\}$	$\frac{4}{5}^{\circ}$	$\left\{ \begin{array}{c} 0.644 \\ \text{to} \\ 1.378 \end{array} \right\}$
11th	$1\frac{3}{5}^{\circ}$	$\left\{ \begin{array}{c} 1.839 \\ \text{to} \\ 1.045 \end{array} \right\}$	$\frac{1}{3}^{\circ}$	$\left\{ \begin{array}{c} 1.045 \\ \text{to} \\ 1.356 \end{array} \right\}$

A slight rise, however, took place at the same period, even when the temperature remained permanent, but then the increase was small in amount.

On the 9th, the temperature fell, but did not oscillate; the fall in the urea was not so great as when the temperature oscillated.

A relationship in the latter part of the sweating stage between the variation in the urea and temperature existed, corresponding to what is stated above. Thus, on the 6th, after the usual oscillation, the temperature had a tendency to fall, and then to remain stationary for some time, and again to fall and remain a second time stationary. During this time the urea fell in quantity slowly. The temperature then took a great fall, and oscillated greatly, and at the same time the fall in urea was very great.

On the 7th the temperature fell slowly, and often remained stationary; at the same time the urea fell slowly, and, like the temperature, did not reach the normal amount till late in the afternoon.

The same close correspondence exists between the other cases.

In order to test still further the relationship between the urea and the temperature, the following method was adopted. The total amounts of urea excreted during the fit, the quantity excreted during the rise and fall of temperature, during the period immediately before the fit, and during the cold and hot stages, respectively, have been added up and divided by the number of degrees the temperature rose or fell in the corresponding periods. By this means the amounts of the urea secreted during the whole and each of the divisions of the fit were reduced to a common standard, and could thus be compared more easily with one another.

Table¹ to show the amount of Urea corresponding to each degree of Fahrenheit of abnormal heat.

Date.	Entire fit. The amount of urea for each degree of abnormal heat.	Rise in the temperature taken, and the amount of urea to each degree.	Fall in the temperature and the urea to each degree.	The quantity of urea to each degree of the temperature before the fit.	The same in the cold stage.	The same in the hot stage.
6th	1·557	0·626	0·930	...	0·339	3·560
7th	1·413	0·615	0·798	0·972	0·391	1·609
8th	1·508	0·903	0·722	2·163	0·735	1·444
9th	1·460	0·675	0·710	0·566	0·246	2·793
0th	1·298	0·718	0·746	0·657	0·617	1·381
11th	1·781	0·712	1·280	0·601	0·590	0·868

¹ In this table each of the quantities of urea correspond to 1° of temperature. In the first column the date is given; in the second, the whole amount of urea passed during the entire fit (the fit being considered to

On comparing the different days, the closest correspondence existed when the whole fit was taken. The extreme in column two being taken, the difference only amounted to one fifth of a degree. The rise and fall also closely corresponded. The extreme again being taken, a difference amounting to one third of a degree was found.

As the duration of the fit might have varied greatly, and so the above mode of comparison of the different days one with the other have been invalidated, the following tables have been worked out.

The first shows the duration of the fit on each day.

6th.....	$7\frac{1}{4}$ hours' duration.
7th.....	8 „
8th.....	$8\frac{1}{4}$ „
9th.....	$7\frac{3}{4}$ „
10th.....	$8\frac{1}{4}$ „
11th.....	$7\frac{1}{2}$ „

commence with the rise of the temperature and the increase of the urea and chloride of sodium). In the third column the rise (in the temperature) only is taken, and when the temperature remained stationary at its highest point for some time the time of the rise is calculated up to the middle of the stationary part. In the next column the fall, calculated in the same way, is given. Then the cold and hot stages are given separately.

The amount of urea varied in this patient; for the night urine varied on one day greatly from the quantity passed during a similar period on other nights. This day, the 9th (the urine of the night before not having been saved), the amount of urea corresponding to each degree was greatly in excess; but on assuming that the quantity passed during the first hour (0·900 grm.) was the quantity normal to him for that day, and so deducting the excess, a close correspondence to the other days resulted. Thus, when the whole amount of urea was calculated as it stood, to each degree 2·043 grms. were found to correspond; but when the additional 300 grms. were deducted, then the quantity per degree was 1·460; and throughout all the different comparisons it will be then found closely to agree. On the 10th, again, the normal excretion was below par (0·170 grm. per hour), which also prevented any comparisons from being made. When this was raised to 0·600 grm., then a much closer correspondence to the other days was found.

Another calculation must now be made. On three days the urine was collected through the previous night; taking that hourly amount, and assuming that to be the amount normal to the man through that day, if there had been no disturbing influences, and deducting that quantity from the quantity passed hourly through the fit, the increase only is obtained, and this divided by the number of degrees the temperature rose, the comparison is then found to be very close.

April 7th.....	0·638	urea to each degree of abnormal heat.
„ 8th.....	0·618	„ „
„ 11th.....	0·624	„ „

If this table be compared with the former one, the comparison will be found to be even much closer. Unfortunately, the amount during the night was not determined except on these three days, so that this mode of calculation is not applicable to all the fits.

On looking at the second column of the table given at page 377, where the total amounts are compared, it is found that on the 6th, 8th, and 11th, the quantity in excess is somewhat over other days. The temperature on the 6th and 8th remained permanent after reaching its highest point. Thus, on the 6th it remained at 105° for two hours and a half; on the 8th at $103\frac{4}{5}^{\circ}$ for one hour and a quarter; but when the amount passed during these permanent periods is deducted, then the urea on the 6th fell to 1·277 grm., and on the 8th to 1·366 grm., bringing each on a level with the 10th. On the 11th, the increase in urea occurred entirely in the fourth column, that is, during the fall of the temperature, the amount passed during the rise corresponding closely to the other days; and on examining the sweating stage on the 11th, there is found a great and sudden increase at its very termination, and this excessive quantity being replaced by the quantity passed on other days at the same period, the amount corresponding to each degree was 1·510, closely coinciding with the other days.

That the increase on the 6th and 8th was due to the above is rendered probable by the following statement: The whole quantity of urea passed on the 6th, during the stationary period of two hours and a half, was 1·957 grm. On the 8th, for one hour and a quarter, the quantity was 1·155. When compared to equal time, that is, the two hours and a half reduced to one hour and a quarter, then, on the 6th, the amount of urea was 0·978, corresponding closely to the quantity passed in the same time on the 8th. From this it would appear that the same amount of urea corresponds to 1° , when the temperature is permanent, whether it be at a high temperature or not, whilst the second table shows that *every degree in the hot stage corresponds to a much greater amount of urea than in the cold or any other stage, whilst the temperature is rising*; thus showing, that the higher the temperature, the more urea corresponds with each rise of a degree than formerly, and thus accounting in some measure for the greater quantity of urea to each degree, when the whole fit is compared, in the more severe fits.

The very close correspondence between the temperature and the urea seems to be thus placed beyond doubt; in fact, the one may be calculated from the other. An example or two will illustrate this.

Thus, on—

April 6th, the amount of urea excreted during the fit was 11·097 grammes; taking 1·503 gramme as the average quantity (all the degrees being taken) corresponding to each degree, this gives a rise of 7° , or a little over; the actual rise was from $98\frac{1}{5}$ to 105, or $6\frac{4}{5}^{\circ}$.

April 7th, the total amount of urea during the fit was 10·635 grammes. The rise in the temperature here should be 7° ; the actual rise was $6\frac{4}{5}^{\circ}$.

April 8th, the total amount of urea excreted was 9·353 grammes, which would imply a rise in the temperature of 6° ; the actual rise was from $97\frac{4}{5}$ to $103\frac{4}{5}$, being exactly 6° .

III. *Chloride of Sodium.*

The chloride of sodium, to a very great extent, agreed with the urea in its relationship to the temperature. Traube's statement on this point is therefore confirmed. For the most part, the remarks above made on the urea hold good for the chloride of sodium; still some differences occurred.

On the 8th, the urea between 7.30 and 8 a.m. remained stationary, whilst the chloride of sodium rose continuously.

9th.—Between 8 and 9 a.m. the urea fell, the temperature corresponding, but the chloride of sodium rose to double its quantity.

Again, during the decline of the fit, they differed on the 8th and 9th; the urea at its termination rose somewhat, whilst the chloride of sodium continued to fall.

The following table corresponds to one given for the urea, and shows the intimate connexion between the severity of the fit and the amount of chloride.

Date.	Entire fit. The amount of chloride of sodium for each degree.	Rise in the temperature taken, and the amount of chloride to each degree.	Fall in the temperature taken, and the amount of chloride to each degree.	The quantity of chloride to each degree of the temperature during the cold stage.	The same during the hot stage.	The same during the period before the cold stage.
6th	0.195	0.085	0.086	0.027	0.293	...
7th	0.225	0.159	0.066	0.085	0.259	0.640
8th	0.171	0.107	0.078	0.131	0.162	0.134
9th	0.241	0.150	0.062	0.175	0.702	0.103
10th			Lost.			
11th	0.180	0.149	0.041	0.102	0.176	0.785

Here, as occurred in the urea, the patient on two days

passed a different quantity normally from what he had on former days; so that on one day, the 8th, it was necessary to add 0.022 grm. to each hour to bring it up to the other days. On the 11th it was necessary to subtract 0.044 grm.

On the 6th the urine was not collected before the commencement of the cold stage, so that the amount for each degree is less than it would otherwise have been in the third and fourth columns.

When the extremes in the third column were compared, a difference corresponding to one third of a degree of temperature occurred. When the fourth column was compared, excluding the 6th, a difference of one third of a degree occurred. In the fifth column, a difference corresponding to less than one third occurred, excluding the 11th, on which day the chloride fell to its normal amount before the fit had ended.

In the cold stage an enormous difference was found.

In the hot the difference corresponded to half of a degree.

Beyond these above differences, all that has been said regarding the urea applies equally to the chloride of sodium.

IV. *Water of the Urine.*

In rising and falling in quantity, the water has a very close correspondence to the urea, though there is very little proportion between the different rises and falls in the two. On the 6th, 8th, and 9th, they corresponded in rising and falling at the same periods. On 11th and 7th the quantity of urine in the hot stage falls so considerably, that in the commencement of the sweating stage a slight rise occurs, this being followed, however, by a decided fall during the second hour.

The quantity of urine thus corresponding to the urea, must, like it, correspond somewhat to the variations in the temperature. That the quantity stands in close relation to the intensity of the fit is seen from the following table.

URINARY EXCRETIONS IN AGUE.

Date. ¹	Quantity of urine in the fit.	Number of degrees temperature rose.	Quantity of urine to each degree.
6th	608 c.c.	$5\frac{1}{5}$	117 c.c.
7th	411 c.c.	$5\frac{4}{5}$	71 c.c.
8th	449 c.c.	$6\frac{1}{8}$	72 c.c.
9th	382 c.c.	$5\frac{2}{5}$	71 c.c.
11th	435 c.c.	$5\frac{4}{5}$	75 c.c.

It has been shown that some correspondence exists between the oscillation of temperature at the commencement of the sweating stage and the fall and subsequent rise in the amount of urea. The following table shows the relationship between the same oscillation and the fall in the amount of urine passed.

On the 6th and 11th it has been said that the amount of urine secreted was so small during the hot stage that it rose somewhat at the commencement of the sweating, so that no comparison can be given on those days between the fall of the oscillation and the quantity of urine. In the next table, in the first column, as usual, the day of the month is given; in the second, the fall of the temperature in the oscillation; in the third, the fall in the amount of urine; in the fourth, the amount reduced to a degree; in the fifth column, the rise of the temperature in the oscillation is given; in the sixth, the rise in the amount of urine in the hour subsequent; and in the seventh, the quantity is reduced to that corresponding to a degree:

¹ In the first column the date is given. In the second, the total quantity of urine passed during the fit. In the third, the number of degrees the temperature rose during the fit. In the fourth, the number of cubic centimetres corresponding to each degree. Excluding the first day, a very close correspondence existed.

6th	Urine rose	...	$1\frac{3}{5}^{\circ}$	0·030	0·020
7th	1° 0·030	0·030	1°	0·017	0·017
8th	$1\frac{3}{5}^{\circ}$ 0·039	0·025	$\frac{4}{5}^{\circ}$	0·025	0·030
11th	Urine rose	...	$\frac{1}{5}^{\circ}$	0·007	0·035

From this limited table, no great correspondence can be traced.

But though the urea, chloride of sodium, and water, thus constantly show a close correspondence to the temperature, the relative amount of rise was different in these three ingredients.

This indeed was shown well during the analysis, in which 10 c.c. of urine were taken; the amount of mercury solution required for the amount of urea varied greatly from hour to hour, showing no regularity of rise; whilst, on the other hand, the amount required in testing for the chloride gradually rose and then gradually sank, often again rising somewhat at the very close of the fit. Thus, to take the 7th of April:

UREA.

Hour.	Amount of mercury solution required for 100 pints of urine.	Same for NaCl.	Hourly amount of water passed.
7 a.m.	298 c.c.	48 c.c.	25 c.c.
8 a.m.	198 c.c.	144 c.c.	80 c.c.
8·30 a.m.	188 c.c.	135 c.c.	136 c.c.
10·30 a.m.	224 c.c.	90 c.c.	62 c.c.
12 noon.	272 c.c.	45 c.c.	33 c.c.
1 p.m.	268 c.c.	45 c.c.	50 c.c.
3 p.m.	248 c.c.	36 c.c.	50 c.c.
5 p.m.	258 c.c.	18 c.c.	28 c.c.

The urea varies in its proportion to the water; thus, during excessive diuresis, the per-centage amount falls, whilst, on the other hand, the per-centage amount of chloride even then increases, up to the time the greatest amount is poured out, then it as steadily falls, even when the water fluctuates

greatly. These remarks apply to the per-centage of chloride of sodium in the urine.

It appears that the amount of urea undergoes an increase definite in amount, independent of the water. The chloride of sodium also undergoes a definite increase, which, also, is independent of the amount of water; but the water being increased, the same per-centage of chloride is poured out as would have been the case if a smaller amount of water had been voided, the per-centage not being lowered by an excess of water, as is the case with urea.

The chloride has thus a tendency to rise and fall steadily, not observing the various alterations corresponding to temperature that the urea does, but the water, corresponding to the urea in this respect, causes variations of the same character in the total amount of chloride poured out.

The time of greatest per-centage excretion of chloride of sodium does not always correspond to the greatest hourly excretion.

Thus, on April 6th, the greatest amount of saturation was at 8 a.m., whilst the greatest hourly excretion was at 8.30, when the water was at its greatest amount.

7th.—The hourly excretion and the per-centage amount agreed in the time at which they occurred, and so also did the water.

8th.—The same occurred on this day.

9th and 10th.—The same occurred also on these days.

11th.—The per-centage amount of chloride was greatest at 9 a.m., whilst the hourly amount excreted was greatest at 10, the water being most abundant during the last period.

The urea, on the other hand, often decreased in per-centage during the fit, especially if the increase in the water was great, its highest per-centage amount corresponding to the lesser amount of water. Thus, on April 6th, the per-centage amount decreased through the entire fit. The decrease was, however, much more gradual at its commencement.

7th.—The greatest per-centage amount was at 7 a.m., the amount of water being 25 c.c. for the hour. The water

then rose to 80 c.c., and the per-centage amount of urea fell; the amount of mercury solution required for 10 c.c. of urine fell from 29 c.c. to 19 c.c. The water then again rose to 136 c.c., and the solution of mercury required fell in amount to 18 c.c. The water next fell to 62 c.c., and the solution of mercury rose to 22·6 c.c. The water again fell to 33 c.c., and the amount of the solution required rose to 27·4 c.c. The water next rose to 50 c.c., and the solution required fell to 26·4 c.c. The water then remained at 50 c.c., but the solution fell to 24 c.c. Then the water fell to 28 c.c., and the quantity of the solution rose to 25 c.c.¹

From these facts it is evident that both the urea and chloride increase, independent of the influence of the amount of water; that any increase in the latter does not modify the aggregate amount of urea, but that it does that of the chloride.

No connexion exists between the quantity of urine passed during the entire fit and the amount of water drunk.

This is seen in the following table:²

Date.	Water drunk.	Urine passed.
6th.....	2135 c.c.....	648 c.c.
7th.....	1335 ,, ...	550 ,,
8th.....	1050 ,, ...	428 ,,
9th.....	500 ,, ...	499 ,,

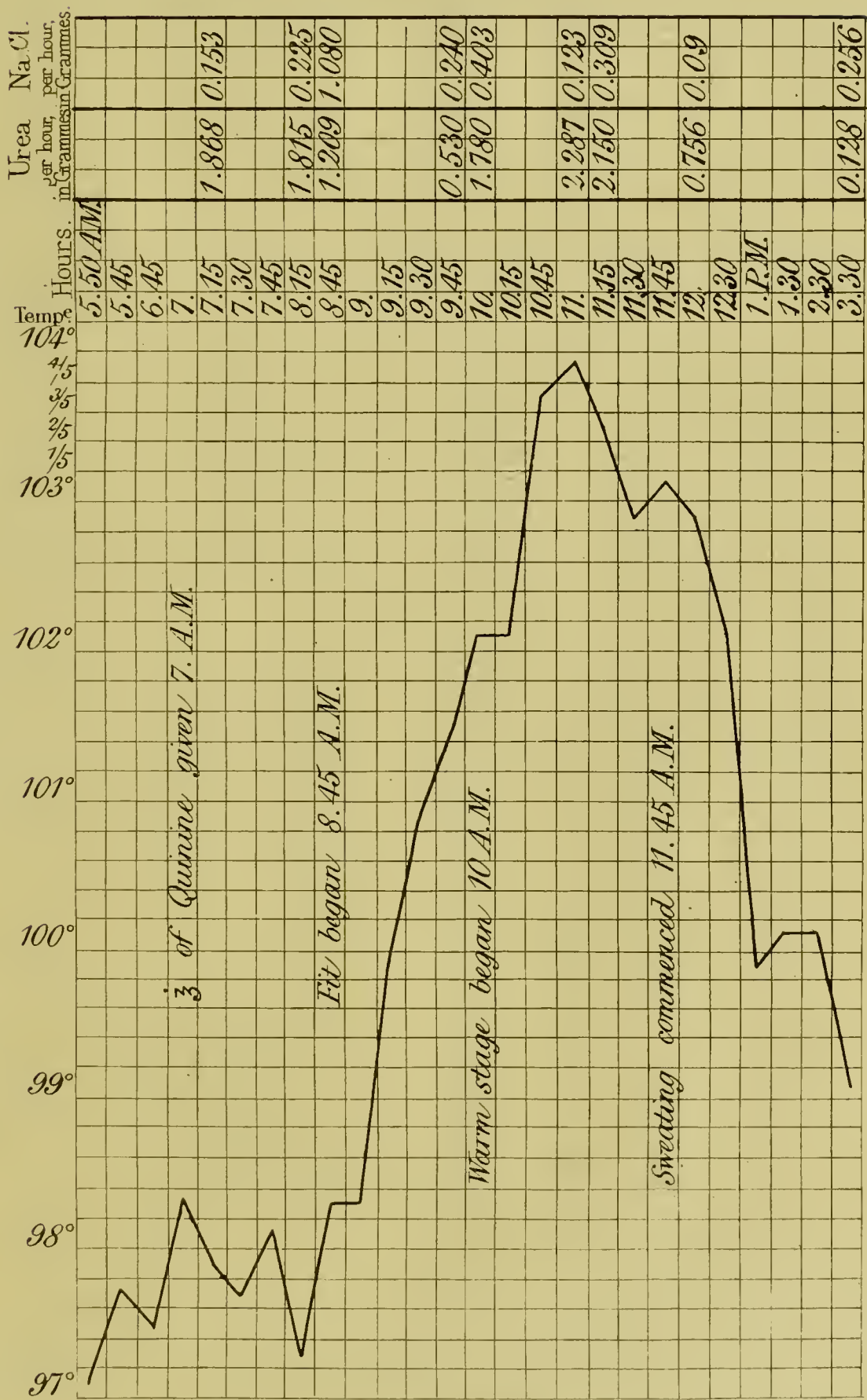
The urine was passed much more equally as regards the different periods than the water drunk, for the entire quantity was mostly drunk during the hot stage only.

Thus, the urine, urea, and chloride of sodium, were independent, to a large extent, of the quantity drunk,

¹ Every c.c. of the mercury solution corresponds to 10 milligrammes of urea.

² As usual, the date is given in the first column; in the second, the quantity of water drunk during the entire fit, and in the third, the amount of urine passed during the entire fit, are given.

APRIL 12TH
Phenomena of a Fit modified by Quinine.



W West. Ind.

though some connexion appeared to exist, as, when the patient drank copiously, the next time the urine was collected it was found to be somewhat in excess; but this might be a mere coincidence.

TABLE.

APRIL 12.—UREA.

Stage.	Hour.	Total Quantity in this time.	Quantity per hour.	Average Quantity per hour during period.
		Grammes.	Grammes.	Grammes.
Before fit	6.15 to 7.15	1.868	1.868	} 1.630
	7.15 to 8.15	1.815	1.815	
	8.15 to 8.45	0.604	1.209	
Cold	8.45 to 9.45	0.530	0.530	} 2.310
	9.45 to 10	0.445	1.780	
Hot	10 to 11	2.287	2.287	} 2.219
	11 to 11.30	1.075	2.150	
Sweating	11.30 to 12.30	0.756	0.756	} 0.442
	12.30 to 3.30	0.384	0.128	

CHLORIDE OF SODIUM.

Before fit	6.15 to 7.15	0.153	0.153	0.153
	7.15 to 8.15	0.225	0.225	0.225
	8.15 to 8.45	0.540	1.080	1.080
Cold	8.45 to 9.45	0.240	0.240	} 0.321
	9.45 to 10	0.100	0.403	
Hot	10 to 11	0.625	0.625	} 0.467
	11 to 11.30	0.154	0.309	
	11.30 to 12.30	0.090	0.090	} 0.173
	12.30 to 3.30	0.708	0.256	

QUANTITY OF URINE PASSED.

Before fit	6 to 7.15	73 c.c.		
	7.15 to 8.15	75 c.c.		
	8.15 to 8.45	54 c.c.		
Cold	8.45 to 9.45	25 c.c.		
	9.45 to 10	84 c.c.		
Hot	10 to 11	125 c.c.		
	11 to 11.30	86 c.c.		
	11.30 to 12.30	32 c.c.		
	12.30 to 3.30	128 c.c.		

On the 12th, everything being conducted in the same manner, upon the temperature commencing to rise, the patient was given $\mathfrak{Dj}$ of quinine, which caused the tempera-

ture to fall again. It continued to fall for half an hour, and then began to rise; the cold stage came on an hour later than on the previous day. The fit, however, was afterwards as severe as usual. The effects on the urea corresponding to this fall cannot be ascertained, as, for some reason, the amount secreted was three times as great as on previous days, for the first two hours it was collected; it then fell somewhat, but continued high throughout the fit, the quantity to each degree being 0·980 grammes.

The temperature obeyed all the rules laid down previously—rising to the commencement of the cold stage; then remaining permanent for half an hour; then rising through the whole of the cold stage, the latter being shorter than the former; and just at the commencement of the hot stage, it again remained stationary for a quarter of an hour; then rose, but began to fall before the sweating stage commenced, and at that point oscillated, the oscillation being small; it then fell rapidly.

The urea corresponded also to these variations, after the manner described. Thus, it fell where the temperature remained stationary, but the fall was out of proportion to the alteration in the temperature, being very great. Possibly, this was due to the quinine. It then rose rapidly, reaching its highest point at the same time as the temperature. It fell slowly during the latter part of the hot stage, then fell greatly during the oscillation at the commencement of the sweating stage; but as the urea did not subsequently rise, the rise in the oscillation of the temperature was only one fifth; then the urea fell greatly.

The chloride of sodium differed somewhat from the urea at the commencement and termination. Thus, though an unusual quantity was passed in the first two hours, like the urea, still it did not fall when the temperature began to rise a second time, but continued rising throughout; just before the cold stage it reached its highest point, arriving at the very unusual quantity of 1·080 grm.

After this it corresponded in its variations to the urea, except in the second hour of the sweating stage, when, instead of continuing to fall, it rose considerably. The rise in the hour subsequent to the oscillation in the temperature was very extensive.

Considering the fit to have commenced on this day, at 7.15 a.m., the amount for each degree was 0.396, a larger quantity (as is also the case with the urea) than occurred on other days; but as the amount passed for some hours before the fit was unusually large, it is probable that the quantity normal for that day was in excess.

The water in its variations corresponded to the urea, except at its very termination (that is to say, the second hour of the sweating stage), when it rose considerably.

The amount for each degree was 105 c.c. It is rendered most highly probable that the reason for the amount for each degree being greater than usual in urea, salt, and water, is, that the normal quantity was in excess on this day, for it is found that the increase in each is proportionate.

The quantity he drank was not taken down on this day. Thus the only influence that can be ascribed to the quinine is the lowering of the temperature and the postponement of the fit.

Examination of the Urine on April 13th, Dij of Quinine having been taken the day before, the fit being entirely absent.

On the 13th no fit occurred. The patient took, without leave, another scruple of quinine the evening before. The temperature remained at 97° the entire day, with very slight variations, never amounting to more than $\frac{2^{\circ}}{5}$. But, notwithstanding this equality of temperature, the urea and chloride of sodium underwent an increase. The urine was collected through the night.

UREA.

CHLORIDE OF SODIUM.

Hour.	Quantity per hour.	Hour.	Quantity per hour.
	Grammes.		Grammes.
3.30 p.m. to 6.30 a.m.	0.610	3.30 p.m. to 6.30 a.m.	0.057
6.30 to 7.30 a.m.	1.340	6.30 to 7.30 a.m.	0.060
7.30 to 8.30 a.m.	1.122	7.30 to 8.30 a.m.	0.082
8.30 to 9.30 a.m.	1.150	8.30 to 9.30 a.m.	0.096
9.30 to 10.30 a.m.	1.412	9.30 to 10.30 a.m.	0.138
10.30 to 11.30 a.m.	0.803	10.30 to 11.30 a.m.	0.086
11.30 to 12.30 p.m.	0.999	11.30 to 12.30 p.m.	0.091
12.30 to 1.30 p.m.	0.606	12.30 to 1.30 p.m.	0.027

Thus, though the patient experienced no change as regards his sensations, and his temperature remained the same throughout the day, *a similar change to that occurring on the previous days was observed in the urea and chloride of sodium.* The fit, as judged by the urine, commenced at 6.30 a.m. The urea then fell somewhat during the next hour, rising again steadily up to 10.30 a.m., when it had reached its highest point. It then fell greatly, and this was followed by a slight rise, and then again fell to the amount normal to this man. The fall, immediately after the first rise, probably corresponded to the termination of the period prior to the cold or the commencement of the cold stage; and had the temperature risen, it would probably at this point have either oscillated or remained permanent for some time.

The next great fall, at 11.30 a.m., corresponded to the sweating stage, and would have been marked in the temperature by a great fall, and then, probably, the temperature would have remained stationary for half an hour, and not have risen, as the subsequent rise in the urea is small in amount. The urea after this small rise again falls to the normal amount.

The chloride also strictly followed the principles laid down, for, as has been shown, it has a tendency to rise continuously, an equal amount of urine being taken each hour, though, if the urine be much altered in

quantity, this salt also falls and rises. Thus, the chloride rises continuously, and is marked by no fall after the first hour, but, corresponding to the great fall of urea at 11·30, it also falls and again rises slightly in the next hour, and then again falls to the amount normal.

The urea and chloride increase *pari passu*, and each reaches its height at the same hour.

The amount of urine, again, corresponded to the urea and chloride of sodium; it fell slightly after the first hour, then rose, reaching its highest point at the same time as the urea; it then fell, but again rose somewhat, and then permanently fell.

3·30 p.m. to 6·30 a.m.....	40 c.c.
6·30 a.m. to 7·30 „	50 „
7·30 „ 8·30 „	46 „
8·30 „ 9·30 „	46 „
9·30 „ 10·30 „	66 „
10·30 „ 11·30 „	41 „
11·30 „ 12·30 p.m.....	51 „
12·30 p.m. to 1·30 „	30 „

Taking the mean quantity of grammes corresponding to a single degree on other days, the increase of urea would correspond to a rise of $5\frac{1}{4}^{\circ}$ in temperature. Thus, as far as the urea, &c., are concerned, the fit was as severe as on previous days.

The urine was again collected hourly during the 14th.

Here the urea and chloride of sodium were again in great excess during the whole day, and also during the night previous.

Hour.	Urea per hour.	Chloride per hour.	Water per hour.
1·30 p.m. to 6 a.m.	1·620	0·168	85 c.c.
6 to 7 a.m.	2·715	0·585	150 c.c.
7 to 8 a.m.	1·332	0·405	90 c.c.
8 to 9 a.m.	2·545	0·877	172 c.c.
9 to 10·30 a.m.	1·106	0·320	67 c.c.
10·30 to 11·30 a.m.	1·107	0·421	78 c.c.
11·30 a.m. to 1·30 p.m.	1·118	0·312	60 c.c.
1·30 to 3·30 p.m.	1·180	0·254	77 c.c.

On the second and fourth hours the urea rose to nearly double the quantity of other hours. After the second rise it remained stationary for two hours, and then rose. This corresponds to some extent with the urea the day before; but after the second rise the fall was not so great, and the subsequent rise was very small in amount.

The chloride more closely resembled the day before. Like the urea of the same day, it rose twice, but the last rise exceeded the first, and was followed by a considerable fall, and this again by a rise of some extent, and then it again fell. The second rise and fall corresponding to the commencement of the sweating stage, the first fall probably would have corresponded (had the temperature risen) to an oscillation or a permanency at the termination of the period prior to the cold stage.

The water closely corresponded to the chloride.

Detracting 1.000 gramme from each hour, that being the necessary quantity to reduce the urea in the night urine to the amount normal to this man, and again, as on the day before, calculating what height the temperature would have reached had it risen, it is found to be 3°.

This fit was therefore less severe than that on the previous day. It thus appears that *variations in the urea and chloride of sodium continue to occur at those periods when, if the fit had continued, the temperature would have risen.* The same fact has been noted by Redenbacher; and it would show that the cure of the fit by quinine, in this man, was followed by a much larger excretion of urea during what would have been the apyretic hours than had been noted at the corresponding time when he was suffering from the disease.

CASE 2.—*Tertian ague.*—The following case of ague occurred in a boy, æt. 19, strong, and in every respect healthy with exception of the attack of ague. The boy had not been out of London for twelve months before, but at that time came over from Dantzic, having been there for some months.

He was admitted into the hospital with the second fit, which was very slightly marked, the fit increasing subsequently in severity till he took four grains of quinine every two hours, which prevented its continuance. It was tertian in type.

Everything was conducted exactly after the manner of the former case. The urine, however, was collected (on one day only) by the stage, and not by the hour. His pulse was taken each quarter of an hour, with the temperature.

The two following charts of the temperature will be found to correspond closely with those given before, the correspondence holding mostly with the severer fits. In the first, the temperature rises slowly up to the cold stage; it then rises rapidly, running up continuously to the commencement of the hot stage, at which point it remains stationary for half an hour; it then runs up to its highest point, remains stationary for a short time, and sinks till the sweating stage commences, when, instead of oscillating, it remains stationary for half an hour, then falls and oscillates, but remains high even at 9 p.m., thus differing from the former and subsequent tables.

This further illustrates the slow rise of the stage previous to the cold one; then its rapid rise, the rise being here also greater than at any other period; also its tendency to be affected first at either termination as the fit becomes less severe. It shows that the temperature falls before the commencement of the sweating stage, and that at this point it either oscillates or remains stationary; and in the severe fit, that the temperature has a tendency to remain stationary at its highest point.

The next chart (that of April 4th) shows the temperature on the day the fit was severer, and consequently we find indications of this in the character and fall of the temperature. It shows at the commencement of the cold stage a tendency to be stationary, but after this it runs up continuously with no permanent period at the termination

of the cold stage, though an approximation is seen in the rise at this point being less than the previous ones. It then remains permanent for some time, and then very slowly sinks, remaining permanent for half an hour just where the sweating commences; the temperature here also falling before the sweating stage commenced. Thus, the continuous rise, the permanency when at its height, and the slow and gradual fall, all indicate the severity of the fit, besides the great height to which the temperature reaches.

The urea, here only estimated for each stage, corresponds to the results before stated. Taking the average amount per hour in the sweating stage as the nearest approach to the quantity normal to the boy, it is found that there is an increase in the period previous to the fit; this continues increasing, is highest during the cold stage, then falls somewhat in the hot, and again falls still lower in the sweating.¹

The same is exactly the case with the chloride of sodium and water.²

The patient drank—

At breakfast	285 c.c.
Before cold stage	200 „
Cold stage	200 „
Hot stage	700 „
Sweating stage	500 „

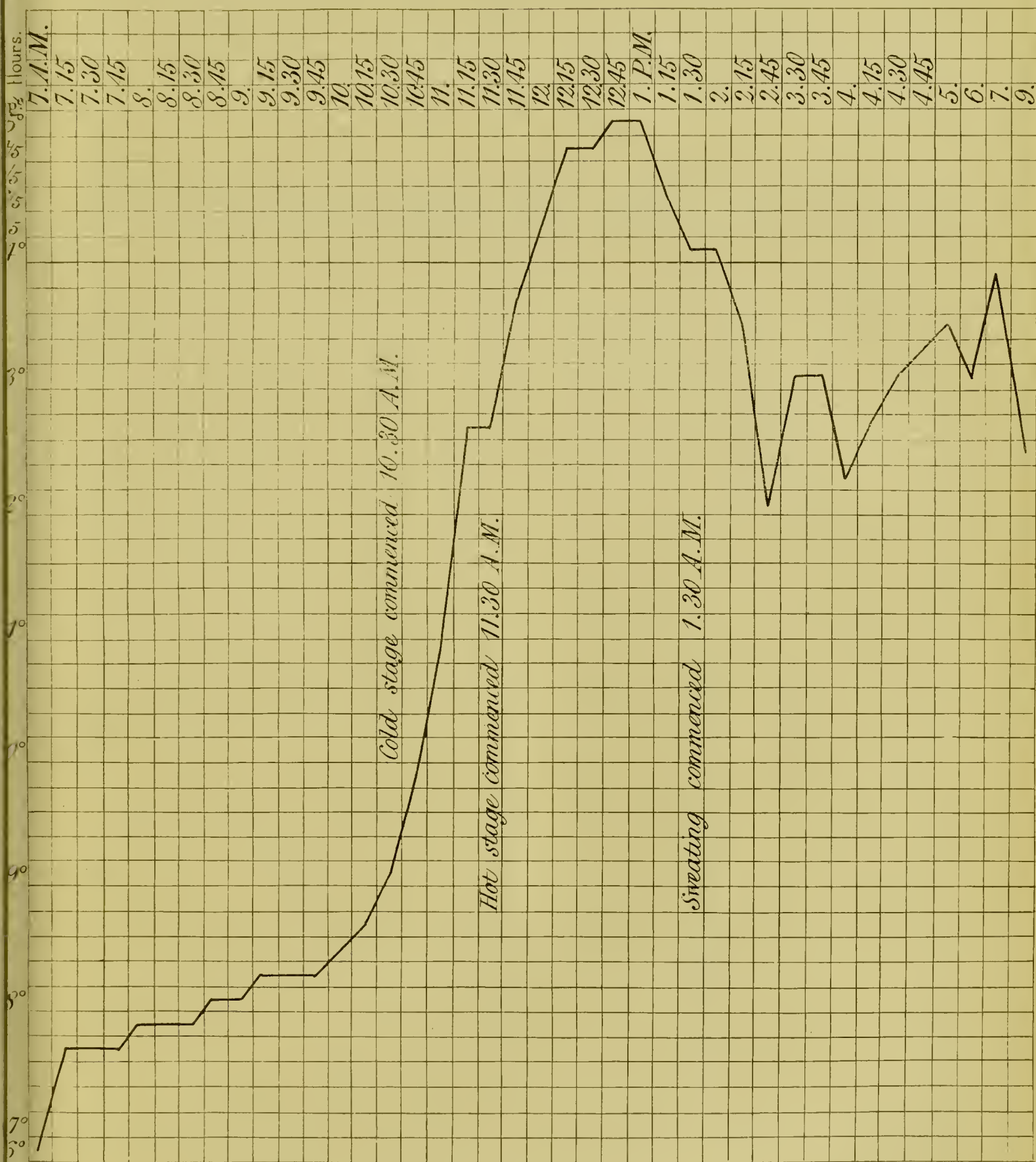
He passed the following quantity of urine :

Before fit (3 hours)	162 c.c. =	54 c.c. per hour.
Cold stage (1 hour)	100 „ =	100 „
Hot stage (2 hours)	180 „ =	90 „
Sweating stage (4 hours) . . .	150 „ =	37½ „

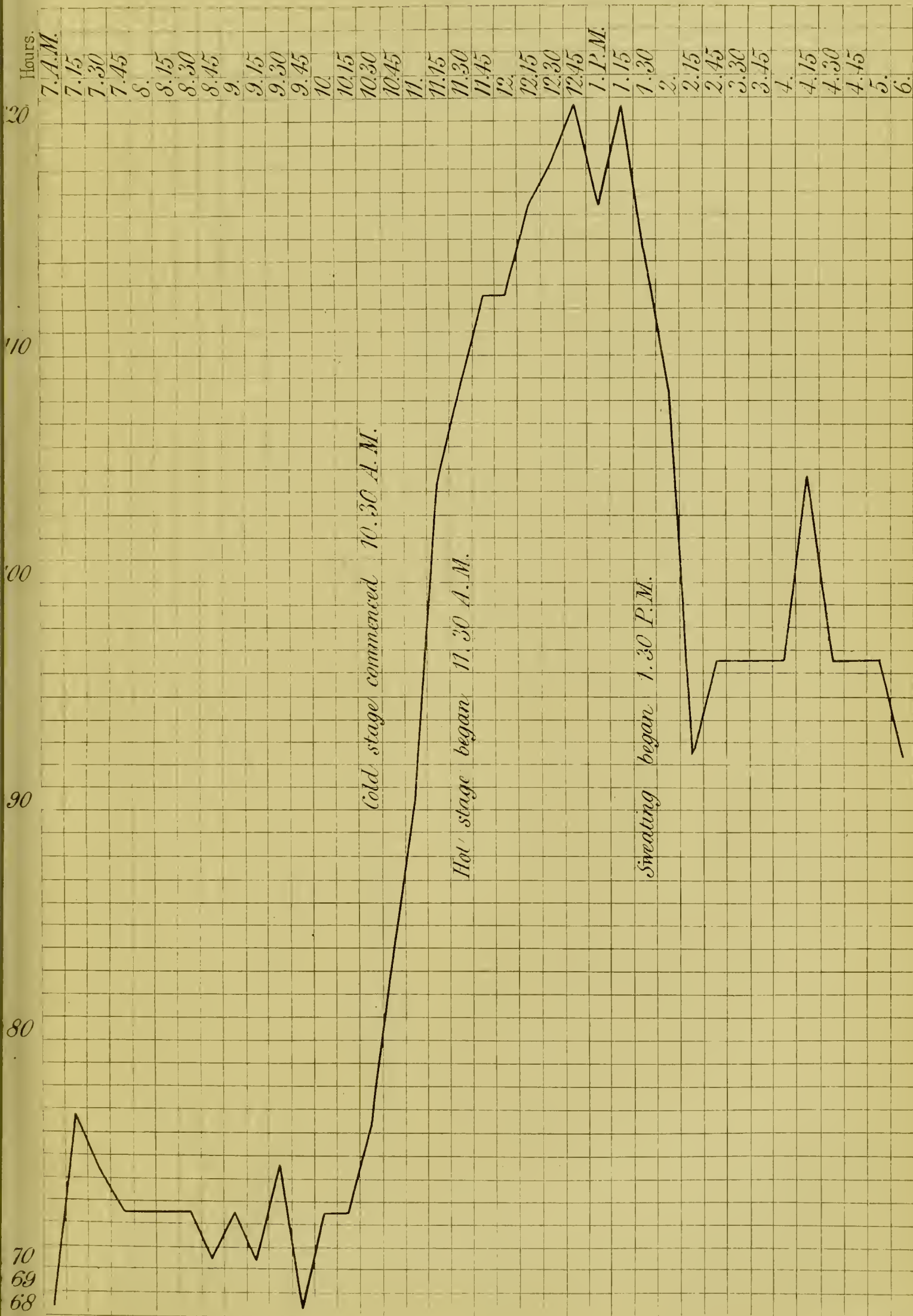
¹ The quantity of urea to each degree was 1·977 grm., showing a close correspondence to the amount for each degree in the former case. The correspondence would probably be closer still if the normal amount of this patient was reduced to that of the former.

² The amount of chloride of sodium corresponding to each degree was 0·502.

APRIL 2ND

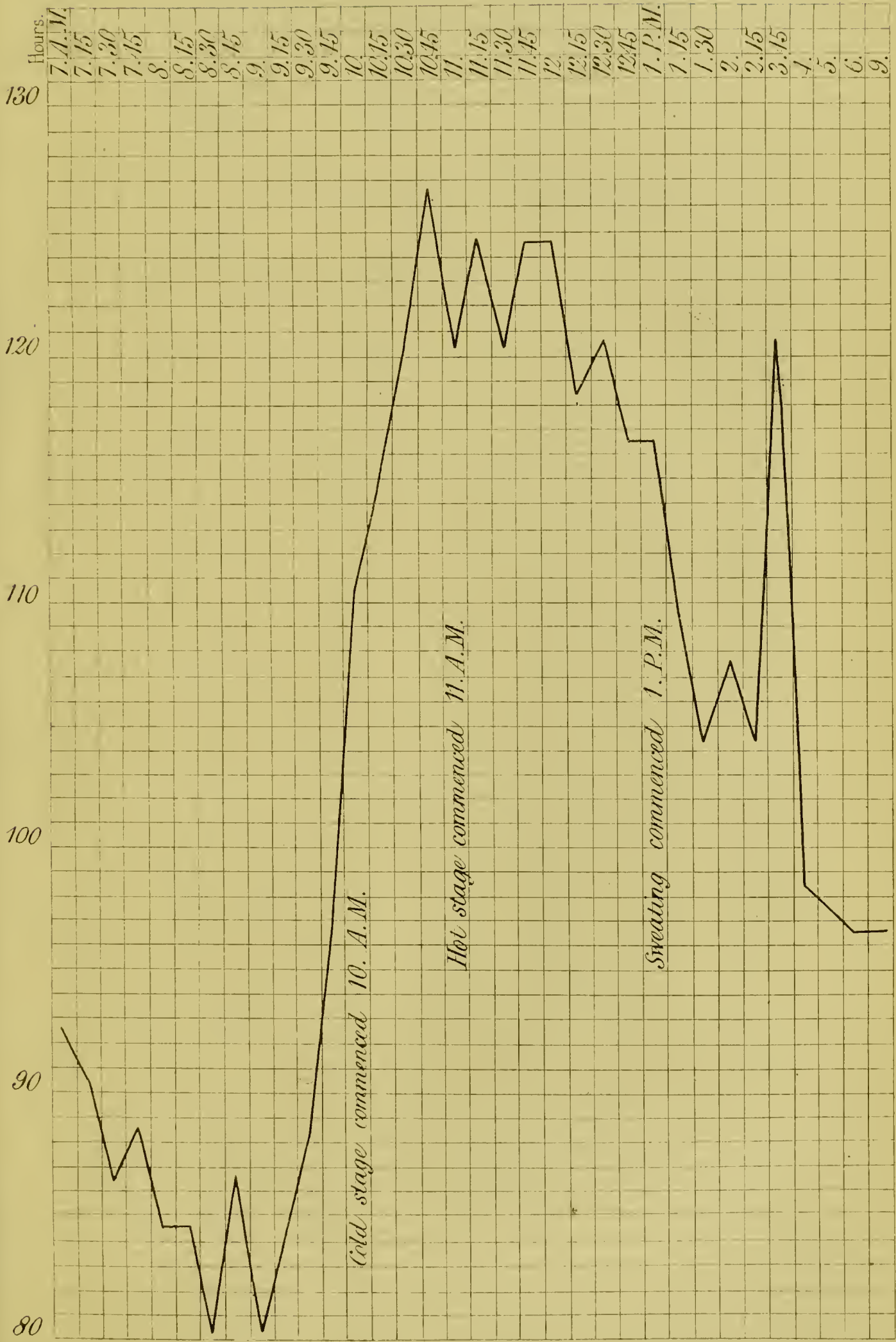


Pulse.



APRIL 4TH

Pulse.



Thus, during the period before the cold stage he drank 323 c.c. in excess over the quantity of urine passed.

Cold stage, he drank 100 c.c. more than he passed ;			
Hot stage,	„	520 „	„
Sweating,	„	350 „	„

making a total of 1293 c.c. in excess of the total amount of urine voided. In this respect, again, he corresponds to the previous patient.

The pulse was taken every quarter of an hour with the temperature in the two fits, and the result is shown in the two following charts. In the first the pulse at the very commencement falls somewhat, and then oscillates. Just before the commencement of the cold stage it commences rising, and then remains stationary for half an hour; then runs up enormously and rapidly during the whole of the cold stage, and at its termination remains again stationary for half an hour; then runs up slightly, oscillates when it has reached its highest point, and immediately on the sweating stage setting in it falls rapidly. In the second chart, at the very commencement, the temperature falls more than it did in the previous one; in the stage previous to the cold it rises more rapidly than in the previous one; runs up still more rapidly during the cold stage, reaches its highest point, and then immediately oscillating, before the sweating stage commences; after oscillating for some time, it falls, and at the commencement of the sweating stage it stands stationary for half an hour, and then falls greatly. During the entire rise there is no tendency for it to remain stationary, still less to oscillate.

This last fit was more severe than the former.

Thus, on both days the pulse commences by falling somewhat, then on both it rises before the fit commences, thus corresponding to the urine and its constituents and also to the temperature. At the commencement of the cold stage, in the less severe fit, the pulse remained stationary for half an hour, and again at the termination of the same stage, whilst nothing of this is seen in the severer one, thus cor-

responding to the temperature, &c. Again, on reaching the climax on both days the pulse oscillates, and the temperature also was unsteady at the same time, though to a much less extent. The pulse commences falling before the sweating stage, and then falls rapidly, more so than the temperature. The pulse, however, fell most rapidly in the less severe case.

Thus, a close correspondence exists between the pulse and the temperature. Like it, the character of the rise varies with the intensity of the fit; it rises before the cold stage commences; then, if the fit is not very severe, remains stationary; again rises through the entire cold stage, the rise being more considerable than during any other period; then falls before the sweating stage, and just at the commencement of this stage stands still for half an hour in the severer cases, and falls subsequently slower than in the less severe cases, in which also there is no stationary period.

CASE 3.—*A case of hectic fever.*—The following well-marked case of hectic is subjoined, on account of its close correspondence to the cases above given.

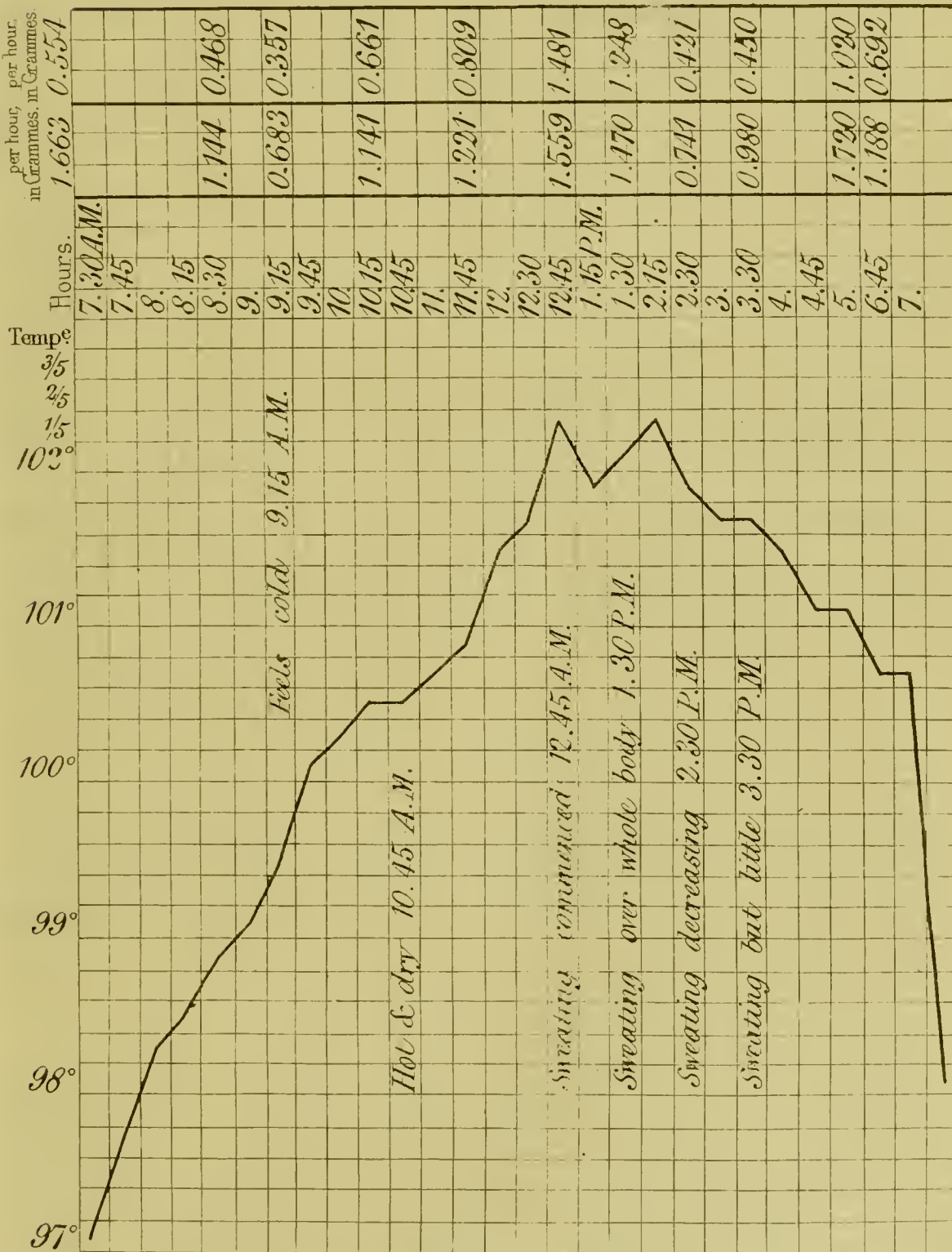
It occurred in a phthisical patient, æt. 45, under Dr. Walshe. It was particularly obstinate in resisting all measures for its removal, and was also peculiar in its occurring always during the day, and its very long continuance, as it commenced at 7 a.m., and continued to 5 p.m. All the stages were unusually well marked, consisting in severe rigors, accompanied with great pain about the loins and legs, the rigors coming on gradually, the sensation of cold being first observed about the feet; the hot and especially the sweating stages followed regularly. The observations were conducted in all respects after the manner of those already detailed.

Temperature.

Here, as in the other cases, the temperature began to rise before the rigors set in, ran up slowly through the

Case of Hectic.

Urea NaCl.
per hour, per hour,
in Grammes, in Grammes



whole of the cold stage, at its termination remained stationary for half an hour, then again ran up slowly, remaining stationary once, till it reached its highest point, when it oscillated, the rise in the oscillation occupying half an hour, then slowly and gradually fell, every now and then remaining stationary. A close connexion exists between this temperature and those given formerly; the rise, however, before the shivering set in was peculiarly great, and the cold stage very short, the rise in this stage not being so much in excess over the other stages as in the cases of ague.

Urea.

Unlike the cases of ague, the urea falls during the period preceding the rigors, and reaches its minimum immediately they set in; the quantity then rises rapidly, and becomes greatest during the hour immediately preceding the sweating stage. The quantity then falls rapidly through the sweating stage, reaching its minimum when the sweating is most severe; then rises again even higher than it was during the hot stage, and after that falls to its normal amount.

Chloride of sodium.

This corresponds to the urea in all respects, except that the rise at the termination of the fit does not equal the amount secreted during the hot stage.

Water

Again corresponds to both the above, except that its greatest quantity was poured out an hour later than the greatest amount of urea and chloride of sodium (showing the independence of these substances one of the other).

The patient was permitted to drink *ad libitum*; the quantity, however, was not measured.

The following table shows the variations in the amount of urinary water :

Hour.	Amount of Water.
7.30 a.m.	93 c.c.
8.30 „	52 „
9.15 „	35 „
10.15 „	58 „
11.15 „	71 „
12.30 p.m.	97 „
1.30 „	104 „
2.30 „	39 „
3.30 „	50 „
5 „	100 „
6.45 „	70 „

The pulse in this patient remained about 80 throughout the day.

GENERAL CONCLUSIONS.

The following are the conclusions deducible from the facts noted in the cases of ague.

Temperature.

1. This rises before the commencement of the subjective fit.
2. The time before the cold stage at which the rise commences varies.
3. It continues to rise during the entire cold stage.
4. The rise during this stage is greater than during any other.
5. It reaches its highest point during the hot stage, but falls again before the sweating stage, the fall being gradual.
6. The fall is more rapid during the sweating stage. The rapidity is in proportion to the slowness of the fit.
7. Definite variations occur in the rise and fall of the temperature indicative of alterations in the severity of the fit.
8. These variations first appear at the commencement and termination of the cold stage.
9. Their earliest indication is seen in a tendency for the later rises in the cold stage to become less extensive.

10. The temperature next becomes stationary for a variable time at either or both extremities of the cold stage.

11. Should the fit become still less severe, the temperature oscillates at these points.

12. An oscillation in the middle of the cold stage indicates a still further diminution in the severity of the fit.

13. Variations also occur during the hot stage.

14. In the severest fits there is a tendency for the temperature to remain stationary at its highest point.

15. If less severe, the temperature immediately falls on reaching its extreme height.

16. When the fits become still less severe the temperature next fails to reach to such a height as previously, but at this point again has a tendency to be stationary.

17. Should the severity of the fit be still less, it just touches the extreme point, and immediately falls.

18. Variations are also observed during the fall of the temperature.

19. Thus, at the junction of the hot and sweating stage, an oscillation, or a tendency to remain permanent, always occurs.

20. In continuing to fall, the temperature either falls gradually and continuously; this occurs in the severe fit—or,

21. Remains stationary every now and then; this indicates a somewhat less intensity of the fit—or,

22. It oscillates; this accompanies the most rapid fall, and occurs during the least severe fit.

23. After sinking to its extreme point, the temperature has a tendency to rise again, the rise being often considerable.

Urea, Chloride of Sodium, and Water.

24. The urea, chloride of sodium, and water, also begin to increase in quantity before the commencement of the cold stage.

25. They continue to rise rapidly, and become most

abundant either at the termination of the cold or the commencement of the hot stage.

26. These urinary constituents commence to fall in amount before the temperature reaches its highest point.

27. During the latter part of the hot stage they decrease in amount slowly.

28. They fall rapidly during the sweating stage, the rapidity of the fall being proportionate to the slowness of the fit.

29. These constituents exhibit variations corresponding to the variations in the temperature.

30. Thus, when the temperature remains stationary at either end of the cold stage, these urinary constituents also remain stationary, or fall somewhat. When the temperature oscillates, the fall in these constituents is proportionately greater.

31. A fall occurs in these constituents corresponding to the oscillation in the temperature at the termination of the hot stage, the fall in their amount corresponding to the depth of the oscillation.

32. A greater diminution in the amount of these constituents is observed when an oscillation occurs, than when the temperature decreases gradually, or tends to remain stationary.

33. The increase in the urea and water is definite, the same amount of increase corresponding to a single degree each day.

34. A greater increase in these constituents corresponds to a single degree at a high than at a low temperature.

35. No connexion existed between the various rises of the urea and chloride of sodium when equal periods were compared together.

36. The urea appeared to be independent entirely of the influence of the amount of water.

37. The chloride of sodium also underwent a definite increase, but this increased per-centage remained the same whatever the amount of water was, so that the total amount of chloride was greatly under the influence of the urinary water.

38. The chloride rose steadily and constantly, and did not observe the variations corresponding to temperature which were seen in the urea, but the water varying with the urea and influencing the chloride, as seen above, caused similar variations in the hourly amount of the chloride.

39. The quantity of water drunk in no way influenced the total amount excreted.

40. The increase in the above constituents often commenced before a corresponding rise in the temperature occurred.

41. The variations in the temperature above described often followed similar variations in the urea, but never preceded them.

42. Quinine given in a single, but large dose, when the temperature commenced to rise, lowered the temperature and postponed the fit for an hour, but had no other effect on that fit, though it prevented its recurrence next day, another scruple having been taken.

43. The pulse corresponded closely with the temperature.

1. "On the alteration of the Pitch of Sound by conduction through different Media." By SYDNEY RINGER, Esq., late Physicians' Assistant at University College Hospital. Communicated by Dr. GARROD. Received November 25, 1859.

Having observed that the pitch of cardiac murmurs underwent various alterations dependent on the constitution of the conducting body, the following experiments were devised to extend and render more certain the observations made on the human subject. In most of these experiments a tuning-fork was used, and in all the alterations in pitch were tested by the ear.

In making these experiments, the note of the vibrating fork was first taken with the instrument close to the ear and without being in contact with any resounding body. It was next placed on the body which was experimented on, and lastly listened to through the medium of the same. The alteration in pitch obtained by these two latter methods gave always the same results in kind, but not in degree, the alteration being always greater when the note was heard through the medium of the conducting body.

SOLIDS.

A board 13 feet long was balanced on the back of two chairs. The note of the fork was then taken, without its being in contact with the board. The fork in vibration being next placed at one end of the board, the ear was placed on the other, and the note was then found to be most appreciably lowered in pitch.

As boards composed of various kinds of wood were not obtainable, tables were used. Of all the woods thus tested, deal lowered the pitch most ; indeed the lowering of the pitch was always in proportion to the porosity of the wood † .

The pitch was found to fall the greater the distance from the fork.

*Bone lowered it.

Glass raised the pitch.

Iron raised it.

† Dr. Wylde, the Conductor of the Philharmonic Society, kindly examined and fully corroborated, in those experiments marked with an asterisk, the conclusions I had previously come to. All the experiments were confirmed by numerous persons of acute ear. In no case was their opinion at variance with my own.

The two last, in conducting the note, greatly lessened the intensity, much more so than the substances described above.

The muscular substance of the heart lowered the pitch. Skin and cellular tissue, on the contrary, raised it.

LIQUIDS.

A large foot-pan was filled with water, and the vibrating fork was partly introduced into this, but as no sound could be heard in this manner without some resounding body, a small circular piece of wood was used for this purpose; the fork placed on this was first listened to; the fork with the piece of wood was then placed under the water; one ear was then immersed in the water, and the note so taken; the pitch was then found to be most decidedly heightened. Any objections to this method of performing the experiment were obviated by the following extension of it. The eyes being firmly shut, any variation in the position of the fork, that is to say, whether it was moved closer to or further from the ear, was accurately determined by the alteration in the pitch.

Next, a glass tube 29 inches long, with a diameter of $\frac{3}{4}$ ths of an inch, was closed at one end, with a diaphragm of gutta percha, oil-silk, or bladder (the same diaphragm being used in each set of comparative experiments). The tube was then filled with the fluid to be examined. The ear being applied to the diaphragm, the stem of the vibrating fork was introduced above into the fluid, care being taken that neither the finger nor the fork was in contact with the glass. Experiments conducted in the above manner gave the following results.

* Water raised the pitch most appreciably.

* Alcohol still higher.

Ether higher.

A solution of protocarbonate of soda of the same specific gravity as the blood, raised the pitch more than pure water.

* A saturated solution raised it still higher.

* Sulphate of baryta, suspended in water, raised it higher than any other tried fluid.

Prussian blue, suspended in water, raised it more than water, but less than the sulphate of baryta.

From the above results it appears that simple fluids heighten the pitch in proportion to their diminished specific gravity, and that the

addition of any substance (though increasing the specific gravity), whether in solution, or merely suspended in the water, heightens it ; that particles in suspension, indeed, heighten it more than solutions.

The fact of different fluids raising the pitch in variable degrees, excludes the possibility of the rise being due to the glass, or any other material used, unless the fluid varying in weight altered the pitch, by affecting the tension of the diaphragm ; but the fact of the alteration in pitch bearing no relation to the specific gravity of the fluid excludes this source of error.

The following experiments were devised to test the influence of running water on the pitch.

Into an india-rubber tube, 13 inches long, and $\frac{3}{4}$ ths of an inch diameter, a funnel was inserted ; immediately below this a small opening was made, just large enough to admit the end of the fork. Water was kept constantly running through this, and the stethoscope (covered with a diaphragm) applied to different parts of the tube ; by this method the pitch was found to be most appreciably raised the further from the fork the stethoscope was applied to the tube. The elevation of pitch was easily recognized at a distance of $2\frac{1}{2}$ inches (the length of the pulmonary artery and adjoining part of the aorta).

The stethoscope having been unfortunately left behind, Dr. Wylde could only apply the ear directly to the tube, and therefore could not speak so decidedly as he did concerning the other experiments, but he was of opinion that the pitch was raised as stated above.

It was next attempted to be ascertained whether the mere motion of the water increased or diminished the rise of the pitch. It appeared that the pitch was very slightly raised by the mere motion of the fluid, the same point of the tube being listened to. The difference in *intensity* was most marked.

The chief object of these experiments being to ascertain the influence of the different constituents of the human body on the pitch of cardiac and other murmurs, and in order that the experiments might, as closely as possible, simulate the actual phenomena in the body, an aorta was tied to the mouth of a tap, and an artificial murmur produced by causing a constriction of the vessel by a piece of twine tied round it. The pitch of the murmur so produced was decidedly raised the further it was heard along the vessel from the point where the sound was generated.

To set the question quite at rest of the possibility of the blood in a vessel raising the pitch, especially at so short a distance as $2\frac{1}{2}$ inches, the following experiment was devised:—A tourniquet was placed over a man's femoral artery, immediately below Poupart's ligament, and an artificial murmur thus produced; this was found to rise rapidly in pitch in passing down the course of the vessel. A well-marked difference was noticed at a distance of only an inch, and decidedly more at a distance of $2\frac{1}{2}$ inches.

The *intensity* of the murmur quickly diminished in passing to the right or left of the vessel, the *pitch* being at the same time rapidly raised, which was due to the interposition of integuments; but this interposition could not be the cause of the rise of the pitch in the course of the vessel, as the murmur could be heard in that direction at a distance of at least 6 inches, whilst it was completely lost at less distance than 2 inches to either side of the vessel; thus the murmur must have been conducted by the blood, whilst the same thickness of integuments was over the artery at the lower and the upper point listened to, for both points were above the place where the sartorius muscle crosses the vessel.

GASES.

If a watch is pressed close to the ear and then gradually moved away, the tick is heard to rise in pitch in proportion to the distance the watch is withdrawn.

*Or, if in place of the watch a tuning-fork be used, the same can be still more distinctly ascertained. Then let the fork, either freely vibrating, or, still better, placed on a resounding board, be moved gradually away from the ear, the pitch will be found to rise the further the fork is carried away from the ear.

An echo of a musical note is higher pitched than the original note. Again, a loud cardiac murmur audible over the entire chest was examined in the following manner:—

The patient was directed first to expire to the utmost, and the pitch of the heart-sound was then ascertained; he was then ordered to inspire to the full; the pitch was then found to be raised. In this experiment, the only variation was an increased amount of air between the point where the murmur was generated, and the ear of the observer.

The substances which lowered the pitch in the above experiments have one common property, namely, porosity, and, as far it could be ascertained, the depression of pitch was in proportion to this condition. Is it possible that the small vacuities included in the substance, acting as resounding cavities, and reflecting the vibrations from their walls, may so direct them that they may somewhat interfere with one another, and thereby be somewhat diminished in number? The following experiment tends in some degree to support this conjecture. It is well known that if the vibrating fork be held obliquely, resting on the table, "a loud resonance is audible; but if the tuning-fork be moved parallel to itself along the surface of the table, the resonance of the table immediately ceases from the interference of the planes of vibration with each other;" but if the fork is moved so slowly, and so that the resonance is not completely destroyed, the pitch falls slightly.

Again, if the fork be applied to the head, and listened to first with the ear open, and afterwards with the ear closed, the pitch is found to be slightly lowered.

In all those experiments in which the pitch was elevated by conduction, it was found that there was diminished *intensity* in proportion to the elevation of *pitch*; thus it would appear that all bodies raise the pitch in proportion to the difficulty with which they receive and conduct vibrations.

Dr. Scott Alison has proved in some recent experiments, that the conductivity of media, as regards rapidity, does not correspond with that of intensity. Of all tried substances, iron was the worst conductor as regards intensity, and this was found to raise the pitch most.

The above explanation is rendered somewhat probable from the fact that in all cases the elevation was greater with a weak note than a strong one. Dr. Wylde tells me that it has long been noticed by musicians that a weak note is somewhat higher pitched than a strong one, it being under these circumstances caught through the medium of the air. Those bodies which, on the contrary, lower the pitch, do so to a greater extent with a weak note.

These explanations are offered with the utmost diffidence, on account of my very limited knowledge of acoustics.

On looking into the literature of the subject, the only reference to alteration of pitch by conduction is that by Dr. Walshe*, who ascribes it to transmission of the vibrations through "varying" media.

* Disease of the Lungs, Heart, and Aorta. 2nd edition, page 151.

ON
THE RELATIVE AMOUNTS OF SUGAR AND UREA
IN THE URINE

IN
DIABETES MELLITUS.

BY
SYDNEY RINGER,
LATE PHYSICIAN'S ASSISTANT AT UNIVERSITY COLLEGE HOSPITAL.

COMMUNICATED BY
RICHARD QUAIN, F.R.S.

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THE observations were made on two patients, inmates of University College, under the care of Dr. Parkes.

In both cases the urea was estimated quantitatively by Liebig's volumetric method. The usual allowance was made for the chloride of sodium, except in the case of Harriet Meader, in whom it was so small in quantity that no allowance was made. The sugar was estimated quantitatively by the copper test. The water is given in cubic centimètres, and the urea and sugar in grammes.

The following points are attempted to be determined.

1. The relation between the excreted amounts of sugar and urea.
2. The influence of starch and sugar on the excretion of urea.

3. The time at which the sugar reached its maximum after a meal.

4. The duration of the influence of a meal.

5. The temperature of the body.

CASE 1.—George Hudson, æt. 30; height, five feet nine inches and a half; weight in health, eleven stone nine pounds. For six months previous to his admission into the hospital he had suffered from symptoms of diabetes, which had increased rapidly in severity, and were strongly marked at the time of his admission. During the first sixteen weeks they continued with unabated activity. After this he improved, and his weight and strength increased. He had some tubercular deposit in both lungs, which had advanced to excavation on the left side. During the early part of the investigation he perspired greatly. During the whole of these observations the patient was purposely kept without medicine. The observations were commenced on October 13th, 1859.

CASE 2.—Harriet Meader, æt. 30, of very diminutive stature. She had suffered ten years previously from diabetes, and was greatly emaciated, though she had been in much the same state during the greater part of her illness. She was almost totally blind from double cataract, and her intellect was greatly impaired. She also suffered from a slight leucorrhœal discharge, so that her urine contained a *minute* trace of albumen, which was removed by amylic alcohol before testing for the sugar, but was not removed previous to testing for urea. During her whole illness she was subjected to no treatment, with the exception of having brown bread in the place of white. Nor was any medicine given her whilst these observations were being made.

1. *On the relation between the excreted amount of sugar and urea.*

After the influence of food on the urine had disappeared

by long abstinence, a constant ratio was found to be maintained between the sugar and the urea. This ratio was 1 of urea to 2·2 of sugar. The ratio is most strictly observed when several hours are compared together in preference to single hours, as the sugar and urea do not exactly correspond in the exact time of elimination. The following tables show the above ratio clearly :

GEORGE HUDSON.
Urine in inanition.

Number of hours since last meal.	Sugar.	Urea.	Ratio of urea to sugar.
9th	4·881	2·582	...
10th	4·772	2·415	...
11th	5·350	2·127	...
12th	5·350	2·127	...
13th	4·545	1·598	...
14th	5·025	2·202	...
15th	3·260	1·560	...
Total	33·211	14·612	1 : 2·2

The same ratio was observed on several other occasions ; not, as above, in several consecutive hours, but for a single hour only. For, on any day that observations were made, a fasting hour was first taken for comparison. Thus :

Number of hours since last meal.	Sugar.	Urea.	Ratio of urea to sugar.
14th	2·453	1·428	1 : 1·7
14th	5·319	2·430	1 : 2·1
13th	3·977	1·680	1 : 2·3
12th	4·825	1·909	1 : 2·5
			Mean 1 : 2·1

HARRIET MEADER.

In the following table three consecutive hours are given.

Urine in inanition.

Number of hours since last meal.	Sugar.	Urea.	Ratio of urea to sugar.
15th	1·631	0·727	1 : 2·2
16th	1·631	0·727	1 : 2·2
17th	1·041	0·456	1 : 2·2

But not only was the above ratio observed during inanition hours, but also after a non-amylaceous and non-saccharine diet; for though both the urea and sugar rose greatly, the same ratio was maintained. Here, again, though, when separate hours are compared, the ratio varies slightly, still the mean ratio is the same as that above given.

HUDSON.

December 30th.—At 10 a.m. he breakfasted on eggs and mutton. He took tea the evening previous at 5, and had nothing between that time and breakfast.

Urine of nitrogenized food.

Hour.	Sugar.	Urea.	Ratio of urea to sugar.
9 to 10 a.m.....	4·324	1·676	1 : 2·5
10 to 11 „	3·856	1·583	1 : 2·4
11 to 12 „	3·604	1·972	1 : 1·8
12 to 1 „	3·604	1·972	1 : 1·8
1 to 2 „	4·181	2·618	1 : 1·6
2 to 3 „	8·214	3·832	1 : 2·1
3 to 4 „	5·851	2·970	1 : 1·9
4 to 5 „	4·427	2·380	1 : 1·8
5 to 6 „	3·437	2·042	1 : 1·6
			Mean 1 : 1·97

January 2d.—He dined at 6.30 on fish, mutton, and eggs. He had taken nothing since the evening previous.

Hour.	Sugar.	Urea.	Ratio of urea to sugar.
6 to 7 p.m.	0.750	0.583	1 : 1.2
7 to 8 „	3.846	2.080	1 : 1.8
8 to 9 „	7.937	3.048	1 : 2.6
9 to 10 „	9.523	3.744	1 : 2.5
10 to 11 „	8.522	3.450	1 : 2.4
11 to 12 „	7.283	3.510	1 : 2.0
12 to 9 a.m.	3.945	2.034	1 : 1.9
			Mean 1 : 2.1

The hourly mean, and not the total amount, is given between 12 p.m. and 9 a.m.

4th.—He dined at 11 p.m. on fish and meat.

Hour.	Sugar.	Urea.	Ratio of urea to sugar.
11 to 12 p.m.	8.695	3.520	1 : 2.4
12 to 1 a.m.	6.818	3.300	1 : 2.0
1 to 2 „	6.607	3.293	1 : 2.0
2 to 7 „	6.666	2.688	1 : 2.4
			Mean 1 : 2.3

Between the hours of 2 and 7 the hourly, and not the total, amount is given.

That some such ratio existed was anticipated on *à priori* grounds, for the sugar, under the above conditions, is probably derived from the nitrogenous elements of the body, and the nitrogen of the albuminous matters which are resolved into sugar must apparently pass off as urea: thus some ratio was probable; for the sugar could only be derived from the nitrogenous or oleaginous constituents of the body. And though reasons have been advanced tending to show that sugar and fat are inter-convertible in these cases, I think it must be admitted that the sugar came from the nitrogenous elements. The fact of the urea

maintaining a constant ratio with the sugar in all its variations, under these circumstances, is strong proof of this. For though it may be said that a certain amount of tissue would be consumed in the conversion of fat into sugar; also that urea being the exponent of this, as the tissue used would be in proportion to the sugar formed, so the urea would hold a constant ratio to the sugar; still, the increase of the urea is much too great to be accounted for in this manner, being often double and treble the amount normal to the patient, which is the exponent of all the changes (secretion, &c.) taking place in the body, and would surely more than equal the loss of tissue required to convert so much fat into sugar.

2. *On the influence of amylaceous or saccharine food on the excretion of urea.*

The excretion of urea appears to be increased after amylaceous or saccharine food, and this independent of the kind of sugar used. The following tables render this probable.

HARRIET MEADER.

December 17th.—The patient dined at 4 on mixed diet. At 12 p.m. eight drachms of cane sugar were given to her.

Hour.	Quantity.	Sugar.	Urea.
9 p.m.....	261 c.c.	14·085	1·357
12 „	220 „	11·000	1·166
1 a.m.....	235 „	13·976	1·222
2 „	282 „	14·100	1·381
3 „	225 „	10·416	1·125
9 „	140 „	7·954	0·840

The above (as is the case with the following) experiment is not so perfect as could have been desired. As it was impossible to keep her without food till the influence of the previous meal had disappeared. Still, the sugar was never given her till the urinary sugar and urea had commenced to decline.

In the above table it is seen that the urea was increased in the second hour after the sugar was taken by 0·220 gramme. The actual increase was much more than this; for the urea would have continued to decrease in amount during these two hours if no sugar had been given, the influence of the previous meal during that time becoming less.

19th.—The patient had taken no food since 11 p.m. the evening previous; at 10 a.m. eight drachms of sugar of milk were given to her.

Hour.	Amount.	Sugar.	Urea.
8 to 9 a.m.	238 c.c.	11·053	1·528
9 to 10 „	107 „	6·079	0·920
10 to 11 „	150 „	8·333	1·120
11 to 12 „	165 „	9·375	1·270
12 to 1 p.m.	102 „	6·071	0·683

19th and 20th.—She dined heartily at 4 p.m. on mixed diet. At 12 p.m. she had eight drachms of sugar of milk given her.

Hour.	Amount.	Sugar.	Urea.
9 to 10 p.m.	101 c.c.	5·295	0·671
10 to 12 „	195 „	9·461	1·482
12 to 1 a.m. ..	255 „	11·590	1·785
1 to 2 „	230 „	10·865	1·610
2 to 3 „	158 „	8·977	1·216

20th and 21st.—The patient dined, as usual, on a mixed diet at 4 p.m., and at 12 p.m. eight drachms of sugar of milk were given to her.

Hour.	Amount.	Sugar.	Urea.
7 to 8 p.m.	305 c.c.	16·576	1·830
8 to 10 „	250 „	12·019	1·550
10 to 12 „	187 „	10·190	1·325
12 to 1 a.m.	210 „	10·744	1·449
1 to 2 „	234 „	10·833	1·544
2 to 3 „	195 „	9·375	1·267

22d.—She breakfasted at 9 on mixed diet. At 1 p.m. eight drachms of glucose were given her.

Hour.	Amount.	Sugar.	Urea.
10 to 11 a.m.	286 c.c.	16·388	1·510
11 to 12	258 „	13·913	1·522
12 to 1 p.m.	55 „	3·197	0·368
1 to 2 „	195 „	11·079	1·092
2 to 3 „	187 „	12·331	0·990
3 to 4 „	130 „	9·027	0·728

On the same day she dined, as usual, at 4 p.m. At 12 p.m. she had eight drachms of glucose given her.

Hour.	Amount.	Sugar.	Urea.
8 to 9 p.m.	243 c.c.	13·522	1·849
9 to 12	253 „	11·727	1·570
12 to 1 a.m.	280 „	12·096	1·820
1 to 3 „	...	5·062	1·582
3 to 9 „	...	6·713	1·203

GEORGE HUDSON.

January 5th.—The evening previous he took a non-amylaceous dinner; consequently the sugar and the urea had nearly reached the ratio observed during inanition hours, and the influence of the meal was much more completely worked off than in the previous tables, thus more correctly showing the actual increase after sugar was taken. Four ounces of cane sugar were given him at 9 a.m.

Hour.	Amount.	Sugar.	Urea.
8 to 9 a.m.	60 c.c.	4·166	1·600
9 to 10 „	126 „	9·834	2·102
10 to 11 „	142 „	12·241	2·101
11 to 12	127 „	11·759	1·778
12 to 1 p.m.	82 „	8·200	0·984

In all the above tables, when more than an hour elapsed before the urine was examined, the total amount of water,

sugar, and urea is not given, but the mean hourly amount.¹

This fact is also well shown on other occasions, in other experiments not devised for this special purpose. Thus, after a hearty non-amylaceous meal, the urea was found to be much less than after a mixed diet, though it may be fairly granted that the amount of nitrogenized food taken was greater in the former than the latter kind of meal. Thus, on December 30th, he took a non-amylaceous breakfast; the highest hourly amount of urea was 3·832 grammes (59 grains). On January 2d he had a similar dinner, and the highest hourly amount of urea was 3·744 (58 grains). On both these occasions he ate most heartily. On October 24th, after a mixed breakfast, the highest hourly amount of urea was 5·3 grammes (82 grains). After a similar tea on the same day, 9·2 grammes (142 grains). On October 28th, after a mixed breakfast, the urea reached 5·355 grammes (83 grains). On the same day, after a similar tea, 7·7 grammes (119 grains) per hour. These are enough for examples, though many others might be given.

The facts above attempted to be established—namely, that during inanition, and also after a meal containing nitrogenous matter, whether combined with amylaceous matter or not, albuminous matter is converted into sugar and urea, and that this is greatly increased by the administration of sugar, and therefore by an amylaceous diet—are quite sufficient to account for the great loss of weight and

¹ In the following case, a patient, æt. 11, under the care of Dr. Hare, half a pound of sugar was given at 12 p.m., the urine having been collected for the two hours previous, and again from 12 p.m. to 7 a.m.

Hour.	Sugar.	Urea.
10 to 12 p.m.	4·049	1·322
12 p.m. to 7 a.m.	12·668	3·230

As usual, the hourly amount is given in the above table.

During the above experiment, the patient took no food between 5 p.m. and 8 a.m. next morning.

In the above table the hourly amounts of sugar and urea are given.

strength in these patients, and the general degeneration of the functions of the body.

It may, perhaps, be said that the increase of the urea, after the administration of sugar, was due to this causing an increase in the amount of urinary water, under which circumstances it is known that an increase of urea takes place.¹ But the increase then depends on previous retention, probably due to a deficiency in the amount of urinary water. Now, it cannot be said that in diabetic patients there is any deficiency in this.

Again, if the increase in the amount of urinary water were the cause of the increase in the amount of urea, there should be a relationship between the two, but nothing of the kind holds, as is seen from the following table, in which the water and urea are given for the twenty-four hours, and the ratio between them also. On all these days the patient took ordinary mixed diet.

HUDSON.

Date.	Water.	Urea.	Ratio of urea to water.
October 17th	5575 c.c.	82·339	1 : 68
18th	5354 „	83·037	1 : 64
19th	5129 „	74·258	1 : 69
February 14th	3805 „	33·454	1 : 115
15th	4042 „	32·336	1 : 126
16th	4400 „	30·800	1 : 146
18th	4000 „	25·600	1 : 160

The first three closely correspond; but, as the water is obviously under the control of the sugar and the urea also, when there is a ratio between the two latter there will of necessity be a relation between the water and urea, and this occurred on the first three days given.

¹ Thus, in a healthy subject, of average height and build, by drinking a pint of water hourly, the amount of urea rose from 2·0 grms. per hour to 4·040 grms. for three hours. During the fourth hour, however, it fell to 3·026. It is true that the usual allowance was not made for the NaCl; but the amount of urinary water was increased enormously, whilst the NaCl suffered no such increase.

The above table, I think, shows indubitably that the increase in the urea is independent of the increase of urinary water, as the ratio between the two varies from 1:68 to 1:160.

On referring to this table, showing the increase in the amount of urea and sugar after a non-saccharine and non-amylaceous meal, it will be seen that an enormous increase in the amount of the urea resulted. It has also been shown that there is probably an increased formation of urea in the body, due to the ingestion of saccharine matter; but the amount of urea eliminated by one or both of these causes may vary in different patients, and in the same patient in different periods of the disease. From the above cases it appears that the condition of the patient depends on the amount of urea, and not on the amount of sugar, eliminated; that, in fact, the improvement of the patient is due to a diminished amount of urea formed, whilst, at the same time, the amount of sugar eliminated may remain the same or be greatly increased.¹ Hudson's case illustrates this. At first he lost flesh with great rapidity, all his symptoms being proportionately severe. The disease continued with unabated severity for nine months. He then apparently remained in *statu quo* for a few weeks, but towards the latter part of the investigation he improved greatly in strength and weight. These variations are well seen in the fluctuations in his weight. Thus, in health he weighed 163 lbs.; January 3d, 107 lbs.; January 26th, 103 lbs.; February 19th, 113 lbs.; February 25th, 113 lbs.

On referring to the following table, it will be seen that coincident with this improvement was an increase in the amount of excreted sugar (this increase was accounted for by an increase in his appetite). But at the same time that this increase in the sugar occurred, a large diminution in the amount of urea took place. Thus, during October, November, and December, he rapidly declined; but in January and February he improved greatly.

¹ Of course, in judging of the increase of the urea in these cases, the amount of nitrogenous food ingested must be considered.

Date.	Sugar.	Urea.
October 17th	324·840	82·339
18th	342·413	83·037
19th	313·091	74·258
January 26th	228·947	29·928
27th	339·285	34·960
28th	231·761	32·637
30th	366·935	41·860
31st	340·357	40·026
February 1st	389·224	30·702
2d	327·307	19·743
3d	281·774	33·542
4th	562·500	42·120
6th	437·900	28·901
7th	420·600	41·639
8th	446·354	44·564
9th	512·000	29·696
10th	456·250	42·705
11th	609·659	40·237
13th	541·666	32·240
14th	413·586	33·454
15th	459·318	32·336
16th	392·857	30·800
18th	313·500	25·600

That the severity of the symptoms is greatly due to the urea is also rendered probable from three other cases, one of which is given above, the other two Dr. Garrod kindly allowed me to take. In all these the amount of sugar excreted was nearly as large as the amount in the case of Hudson during the most severe part of his disease (October), but the amount of urea was very much less, and at the same time their condition was stationary, and had been so over a period of about ten years.

The following table shows the daily amount of sugar and urea in the case of Harriet Meader, on mixed diet.

Date.	Sugar.	Urea.
December 16th	189·435	23·300
17th	248·504	26·098
18th	238·712	33·653
19th	257·475	30·196
23d.....	247·589	33·885

Dr. Garrod's cases were taken for only one day each ; they gave the following amount of sugar and urea :

	Sugar.	Urea.
1st.....	295·454	39·000
2d	264·309	32·374

The variation in the amount of urea in different patients, and in the same patient at different periods of the disease, may be due either to a lessened influence of the ingested sugar or to a diminished amount of nitrogenous matter resolved into sugar and urea, independent of the influence of sugar (which we have seen occurs), or, as is probable, it may be due to both causes combined.

This twofold origin of urea will readily account for their enormous appetite ; for the chief part of the albuminous matter ingested being resolved into urea and sugar, proportionately less will be left to nourish the tissues, and if the entire amount of nitrogenous matter should be eliminated, then we can understand how it is that they experience a sense of hunger immediately after a meal. And if it be established that the ingestion of sugar has the power to increase the resolution of albuminous matters into urea and sugar, it is conceivable that the amount thus resolved may be even greater than the amount taken in as food ; then the blood or other tissue will be attacked, and the meal will then leave the patient in a worse condition than it found him.

These facts also explain how it is that abstinence from amylaceous matter, as food, is often followed by such good results.

The urea in Hudson's case increased after a meal, corresponding, in this respect, to the increase that occurs in health, except as regards amount ; and there can be little doubt, I think, that the increase in his case was due to the same causes that operate in health. But as the sugar increased also in his case, maintaining the ratio mentioned above, after a non-amylaceous meal, if it can be shown from

whence the sugar is derived it will also show the origin of this rise in the urea.

Now, as regards the increase of the sugar, there are two conceivable sources—1st, the tissues (retrograde metamorphosis); 2d, some organ, by its function, resolving nitrogenous matter into sugar and urea, which function, in diabetes, is altered, so that the sugar is less highly elaborated, and thus non-consumed.

Again, the sugar during inanition periods, and the increase after a non-amylaceous meal, are probably derived from the same source.

The chief difficulty in settling this question lies in the difficulty of proving whether any of the sugar, either taken in *ab externo*, or formed in the body, is consumed, or whether all is thrown off (as far as these cases are concerned).

There are reasons for thinking that some is consumed; thus, the enormous rise in the temperature after a meal would seem to point to this conclusion, though, as the diet in all these cases was mixed, it might have been due to oleaginous matters, taken in in unusually large amount. On the other hand, there are some rather strong reasons for thinking that all the sugar was thrown off. For, though the temperature rose so highly after food, this did not stand in proportion to the amount of amylaceous food taken; thus the temperature reached its highest after dinner, when the nitrogenous and oleaginous elements were in excess, the patient then taking much less bread. On October 24th, after dinner, it reached 101° ; the same evening the temperature rose nearly as high as $100\frac{2}{5}^{\circ}$, but he had a meat tea; he ate, however, much more bread than at dinner. On October 27th he had a very good breakfast, but only toast and tea; the temperature reached $99\frac{3}{5}^{\circ}$. And on the 28th, after a very good tea, it reached only $99\frac{4}{5}^{\circ}$, and it must be remembered that he took butter with his bread at breakfast and tea, so that would, perhaps, account for the great rise, even then.

Again, as there is a constant ratio between the sugar and

the urea during inanition and after a non-amylaceous diet, it is obvious that if any is consumed it must be complete up to a certain point, and after that in a constant ratio; if this applies to sugars formed in the body, it probably applies to all. If so, it is evident that there should be a relationship between the sugar excreted and the temperature (if the former is the cause of the rise of the latter); or if the temperature is due to the sugar consumed, and this again holds a constant proportion to that excreted, the excreted amount will hold a proportion to the temperature; but there is not the slightest relationship between the two. It may be said that both the sugar and the oleaginous matters were concerned in the elevation of the temperature, and as the proportion of the two to one another, in the food, varied, so no relationship would exist between the sugar and the temperature. But admitting the force of this, still, if any were due to the sugar, there could not be so great a discrepancy as constantly exists between the temperature and the sugar, no vestige of a relationship existing between them. This is well seen by looking at the diagrams, where it will be observed that, on October 24th, at 3 p.m., the temperature stood at 101° , whilst the sugar amounted to 17 grammes per hour. At 10 p.m. the temperature stood at $100\frac{2}{5}^{\circ}$; the sugar had reached 37 grammes per hour.

27th.—The temperature at 11 a.m. was $99\frac{2}{5}^{\circ}$, and the sugar stood at 30 grammes.

28th.—At 9 p.m. the temperature showed 99° . The sugar reached 31 grammes per hour.

It thus appears to me that the temperature cannot be taken to prove that any of the sugar is consumed, indeed, the inference is in the other direction.¹

It may be that some of the sugar taken in *ab externo*

¹ There is, however, another conceivable cause of the rise in the temperature. Thus it is known that at least some of the sugar ingested is converted into lactic acid in the alimentary canal, and being absorbed as such would be consumed, and cause an elevation in the temperature. (See Lehmann's 'Physiological Chemistry,' translated by the Cavendish Society.)

was consumed, whilst all that formed in the body was excreted. If this be granted, it is all that is required for the present purpose.

When abstinence of food was continued long enough, in both cases the ratio between the sugar and the urea was lost, that is to say, the urea ceased to fall, whilst the sugar still did so. Thus, in Hudson's case, on January 2d, the following occurred :

Hour.	Sugar.	Urea.
1.30	2.884	1.320
3	1.384	1.100
5	0.635	1.000
7	0.750	0.583

MEADER.

1.30	1.291	0.574
2.30	0.852	0.567
3.30	0.961	0.700

Now, if no sugar is consumed, to what is the excess, just at this point due? If the sugar is due to some organ acting on the albuminous constituent of the blood, and not due to the retrograde metamorphosis of the tissues, we should have a small amount of urea to be accounted for in this manner; and whilst the sugar and urea are very large in quantity, this would be insufficient to affect the ratio to any appreciable degree; but when the sugar and urea become much reduced, then the urea would be found in excess, as we find it here. For if the sugar is derived from the retrograde metamorphosis of the tissues, then they should fall, *pari passu*, maintaining the usual ratio. Thus I think we are driven to admit that the sugar is due, in these cases, to some organ which is endowed with this function; and even if some of the sugar was derived from the tissues by retrograde metamorphosis, the liver must have been at fault likewise. As it is known that it is here that ordinary sugar

is rendered available for the body, and as it is also known that the liver has the power of forming sugar from nitrogenous substances, it is more compatible with reason to ascribe the entire disease to the liver than to distribute it between it and the rest of the body.¹

Thus, having shown it probable that the sugar in these cases was due to the function of the liver, it is of course in an equal degree probable that the rise of urea after a meal is due to the same organ.

From what has gone before in this paper, I think it appears that the excretion of urea from the influence of amylaceous food, and the excretion due to nitrogenous food, though mostly combined, are not necessarily so; that the sugar taken in may pass off unchanged, whilst the nitrogenous matters remain unattacked; but whether the reverse may occur is, perhaps, doubtful,² though conceivable. But besides these two possible forms of diabetes, there is probably a third, namely, the tissues which by altered retrograde metamorphosis, yield diabetic sugar and urea instead of their ordinary products.

Any theoretical consideration as to the nature of the lesion (in cases similar to those given above), based solely on the non-consumption of the sugar, if not erroneous, must be incomplete, as it is necessary to consider the excessive formation of sugar in the body. Thus we may reject as at

¹ Again, the liver (as is well seen in carnivora) forms sugar at the expense of the albuminous constituents of the body, the nitrogen of which must pass off as urea; and as we find an increased formation of sugar by the liver after a meal, so should we expect a corresponding increase in the amount of urea in the urine. Dr. Parkes, moreover, has endeavoured to show that in cases of abscess of the liver, with great loss of liver-tissue, the amount of urea is diminished. Another probable cause of part of the increase is the products of retrograde metamorphosis taken in with muscle, &c., as food, for we know the juice of flesh contains creatine and creatinine, &c. These would probably be absorbed to some extent, and some would pass on to the formation of urea.

² Since the above was written I have met with three cases which render it possible that such may be the case.

least insufficient Miahle's view, that the disease is due to an insufficient amount of alkali in the blood; also any views that look to the respiratory organs as at fault; as also any view that merely considers the disease due to mal-assimilation of sugar in the intestinal canal; and further, any system of treatment founded on such views must be received with caution.

3. *On the time at which the sugar reached its maximum in the urine after a meal.*

This varies according to the nature of the food and the stage of the disease.

Mixed diet:

HUDSON.

During the early experiments it reached its maximum during the third or fourth hour.

Date.	Hour.		
	Breakfast.	Dinner.	Tea.
October 17th	3d	—	—
18th	4th	2d	—
21st	—	—	3d
24th	—	—	4th
26th	3d	—	—
27th	4th	—	—
28th	4th	—	—

Later in the disease it reached its highest during the sixth hour.

January 6th.....6th.

January 13th.....6th.

Sugar in solution (both cases) reached its maximum at the second hour, with one exception, when the maximum was reached during the first hour.

In these observations the time occupied in eating the meal is included.

Pure albuminous diet :

Date.	Hour.		
	Breakfast.	Dinner.	Tea.
November 2d.....	—	4th	—
December 29th	—	4th	—
January 2d	—	4th	—

4. *Duration of the influence of food (mixed diet).*

The duration of the influence of mixed diet was longer towards the latter part of the observations.

October 19th.—Tea between 5 and 6 p.m. All effect of the meal had disappeared at 2 next morning, that is to say, the starvation ratio was reached by that time ; but on December 28th the influence still existed after thirteen hours had elapsed, and might have continued longer, but the patient could wait no longer. In this woman the influence lasted fifteen hours. Thus it would appear, as might have been expected, that the digestive powers became impaired.

The urea had a tendency to pass off sooner somewhat than the sugar, possibly because it is more pernicious.

The increase of the sugar in the urine due to the influence of the meal lasted longer than the increase in the urea.

The above statements will be found to be correct on referring to the tables appended, in which the entire observations are given.¹

¹ Besides the sugar and urea, the amount of urinary water in all cases is given ; also in many cases the chloride of sodium, and in a few cases the specific gravity. No reference has been made in the previous pages to these constituents, as the observations were not sufficiently numerous.

HUDSON.

Till October 20th he was allowed to take what food he chose. This consisted of bread and butter, tea or cocoa, with sugar and milk, for breakfast. Meat, bread, and potatoes, with half a pint of porter, for dinner. His tea corresponded to his breakfast.

October 14th.—Breakfasted at 8·30; dined at 1; tea at 5.

15th.—Breakfasted at 9; dined at 1; tea at 5.

16th.—Breakfasted at 9·15; dined at 1; tea at 6.

17th.—Breakfasted at 8·30; dined at 1.

18th.—Breakfasted at 9; dined at 1; tea at 6.

19th.—Breakfasted at 9; dined at 1; tea at 5·30.

20th.—Breakfasted at 8.

OCTOBER 13TH.

Hour.	Quantity.	Sugar.	Urea.	NaCl.	Sp. gr.
9 to 10 p.m.	390 c.c.	...	4.524	...	1042
10 to 11 "	355 "	...	4.473	...	1042

OCTOBER 14TH.

11 p.m. to 8 a.m.	1115 c.c.	...	23.192	6.244	1050
8 to 9 a.m.	60 "	...	1.710	0.300	
9 to 10 "	205 "	...	3.895	0.820	
10 to 11 "	310 "	...	4.030	1.054	
11 to 12 "	330 "	...	2.640	1.386	
12 to 1 p.m.	295 "	...	2.006	0.914	
1 to 2 "	367 "	...	3.596	1.388	
2 to 3 "	335 "	...	3.886	1.239	
3 to 4 "	247 "	...	3.507	0.666	
4 to 6 "	377 "	...	7.351	1.508	

OCTOBER 15TH.

6 p.m. to 8 a.m.	2600 c.c.	...	36.920	8.840	
8 to 9 a.m.	50 "	...	1.300	0.185	
9 to 10 "	80 "	...	2.136	0.320	
10 to 11 "	150 "	...	2.775	0.330	
11 to 12 "	265 "	...	3.445	0.530	
12 to 1 p.m.	265 "	...	3.445	lost	
1 to 2 "	333 "	...	3.996	1.198	1042
2 to 3 "	315 "	...	4.095	1.102	1043
3 to 4 "	265 "	...	4.081	0.715	1047
4 to 5 "	180 "	...	3.366	0.480	1051
5 to 6 "	225 "	...	4.320	0.832	1048
6 to 7 "	280 "	...	4.844	1.164	1047
7 to 8 "	350 "	...	4.865	1.120	1043
8 to 9 "	275 "	...	3.575	0.825	1045

OCTOBER 16TH.

9 p.m. to 8 a.m.	1480 c.c.	...	23.680	6.600	
8 to 9 a.m.	50 "	...	1.270	0.225	
9 to 10 "	88 "	...	2.041	0.440	
10 to 11 "	220 "	12.200	3.580	0.572	
11 to 12 "	290 "	16.111	3.915	0.870	
12 to 1 p.m.	295 "	17.987	3.953	1.357	
1 to 2 "	360 "	25.714	4.080	1.476	
2 to 3 "	250 "	15.625	3.025	1.075	
3 to 4 "	397 "	20.253	5.161	3.295	1041
4 to 5 "	215 "	15.808	3.289	1.258	1050
5 to 6 "	215 "	14.527	3.504	1.225	1051

OCTOBER 17TH.

6 p.m. to 8 a.m.	2225 c.c.	163.603	36.295	17.132	1049
8 to 9 a.m.	127 "	7.434	2.870	1.143	1051
9 to 10 "	225 "	14.423	3.487	1.755	1045
10 to 11 "	265 "	16.562	2.982	2.252	1040
11 to 12 "	590 "	26.339	6.608	3.304	1040

OCTOBER 17TH—*continued.*

Hour.	Quantity.	Sugar.	Urea.	NaCl.	Sp. gr.
12 to 1 p.m.	515 c.c.	23.842	6.025	3.399	1038
1 to 2 „	400 „	18.181	4.880	2.600	1036
2 to 3 „	465 „	16.146	5.673	3.441	1035
3 to 4 „	330 „	16.176	4.851	1.710	1040
4 to 5 „	215 „	13.109	4.178	0.838	1045
5 to 6 „	215 „	9.045	4.493	1.075	1050

OCTOBER 18TH.

6 p.m. to 8 a.m.	2535 c.c.	147.384	43.095	9.126	1046
8 to 9 a.m.	52 „	2.453	1.428	0.273	1050
9 to 10 „	172 „	12.647	3.698	0.584	1045
10 to 11 „	255 „	16.346	3.493	0.994	1039
11 to 12 „	380 „	25.000	4.408	1.444	1040
12 to 1 p.m.	407 „	28.208	4.354	1.465	1039
1 to 2 „	443 „	24.611	4.562	1.993	1042
2 to 3 „	400 „	33.333	4.520	1.200	1045
3 to 4 „	270 „	15.000	3.591	1.215	1044
4 to 5 „	325 „	18.460	5.037	1.430	1040
5 to 6 „	315 „	13.815	4.851	1.795	1040
6 to 7 „	195 „	10.156	3.315	0.936	1048
7 to 8 „	270 „	21.094	3.051	0.864	1047
8 to 9 „	327 „	26.435	4.152	1.113	1046

OCTOBER 19TH.

9 p.m. to 8 a.m.	1510 c.c.	92.037	26.275	6.946	1049
8 to 9 a.m.	100 „	5.319	2.430	0.750	1050
9 to 10 „	95 „	5.525	2.004	0.351	1050
10 to 11 „	237 „	17.426	3.578	0.616	1045
11 to 12 „	327 „	18.055	4.087	1.012	1042
12 to 1 p.m.	345 „	19.166	3.795	1.301	1040
1 to 2 „	388 „	22.558	4.362	1.590	
2 to 3 „	440 „	22.000	5.325	2.288	
3 to 4 „	395 „	21.944	4.891	2.409	
4 to 5 „	290 „	16.122	3.944	1.524	
5 to 6 „	250 „	15.244	4.050	1.175	
6 to 7 „	228 „	17.272	3.898	0.661	
7 to 8 „	313 „	22.357	4.695	0.939	
8 to 9 „	380 „	29.688	4.332	1.140	
9 to 10 „	435 „	21.750	5.176	1.696	
10 to 11 „	383 „	21.277	4.251	1.532	
11 to 12 „	342 „	21.625	4.856	1.675	

OCTOBER 20TH.

12 to 1 a.m.	248 c.c.	12.917	2.429	1.288	
1 to 2 „	207 „	11.500	2.607	1.304	
2 to 3 „	123 „	4.881	2.583	1.210	
3 to 4 „	105 „	4.772	2.415	0.987	
4 to 6 „	197 „	10.701	4.255	1.635	
6 to 7 „	72 „	4.545	1.598	0.597	
7 to 8 „	97 „	5.052	2.201	0.834	
8 to 9 „	60 „	3.260	1.560	0.510	

For the tables on Oct. 26th, 27th, and 28th, the reader is referred to the diagrams.

December 28th.—Dined between 12 and 1 ; ordinary diet. Tea at 5.15 ; ordinary diet. At 6.45 he took some milk.

29th.—6 a.m., he took a non-amylaceous breakfast. Tea at 5.

30th.—Breakfasted between 9 and 10, on a non-amylaceous meal. He took nothing from that time till 6, when he dined on a mixed diet.

31st.—He took only breakfast and dinner, the latter at 6 p.m.

January 2d.—Breakfasted at 9, on a non-amylaceous diet ; but scarcely ate anything till 6 p.m., when he ate a hearty dinner, composed of non-amylaceous matter.

4th.—He took nothing from breakfast till 6 p.m., when he took a pint of milk. At 11 p.m. he ate heartily of meat alone.

5th.—9 a.m., he took two ounces of cane sugar.

DECEMBER 28TH.			
Hour.	Quantity.	Sugar.	Urea.
4 to 5 p.m.	308 c.c.	22.000	4.312
5 to 6 „	312 „	22.941	4.368
6 to 7 „	510 „	36.428	5.304
7 to 8 „	305 „	22.426	3.233
8 to 9 „	252 „	20.321	2.973
9 to 10 „	394 „	30.781	4.275
DECEMBER 29TH.			
10 p.m. to 5 a.m.	1860 c.c.	122.368	26.412
5 to 6 a.m.	122 „	8.714	2.293
6 to 7 „	107 „	7.037	2.204
7 to 8 „	105 „	6.907	2.268
8 to 9 „	98 „	6.447	2.254
9 to 6 p.m.	2160 „	154.285	35.424
6 to 7 „	363 „	23.881	5.445
7 to 8 „	345 „	20.535	5.106
8 to 9 „	190 „	11.046	3.268
9 to 12.30 a.m.	567 „	35.437	11.907
DECEMBER 30TH.			
12.30 to 8 a.m.	580 c.c.	45.312	13.456
8 to 9 a.m.	62 „	5.000	1.475
9 to 10 „	64 „	4.324	1.676
10 to 11 „	57 „	3.856	1.503

DECEMBER 30TH— <i>continued.</i>			
Hour.	Quantity.	Sugar.	Urea.
11 a.m. to 1 p.m.	124 c.c.	7.208	3.944
1 to 2 p.m.	77 "	4.181	2.618
2 to 3 "	138 "	8.214	3.832
3 to 4 "	110 "	5.815	2.970
4 to 5 "	85 "	4.427	2.380
5 to 6 "	66 "	3.437	2.042
JANUARY 2D.			
9 p.m. to 7.30 a.m.	2320 c.c.	45.238	26.216
7.30 to 8.30 a.m.	78 "	4.642	1.255
8.30 to 9.30 "	124 "	9.687	1.996
9.30 to 10.30 "	120 "	8.571	1.920
10.30 to 11.30 " ..	110 "	7.432	1.980
11.30 to 12.30 p.m.	87 "	5.178	1.705
12.30 to 1.30 "	60 "	2.884	1.320
1.30 to 3 p.m.	64 "	2.077	1.651
3 to 5 p.m.	61 "	1.270	2.000
5 to 7 "	72 "	1.500	2.332
7 to 8 "	80 "	3.846	2.080
8 to 9 "	127 "	7.937	3.048
9 to 12 "	160 "	9.523	3.744
10 to 11 "	150 "	8.522	3.450
11 to 12 "	134 "	7.283	3.510
12 to 9 a.m.	625 "	35.511	18.312
JANUARY 4TH.			
7.30 to 8.30 p.m.	503 c.c.	26.198	9.355
8.30 to 11 p.m.	500 "	22.727	8.950
11 to 12 "	160 "	8.695	3.520
JANUARY 5TH.			
12 to 1 a.m.	150 c.c.	6.818	3.300
1 to 2 "	185 "	6.607	3.293
2 to 7 "	640 "	33.333	13.440
7 to 8 " ..	153 "	10.066	3.457
8 to 9 "	60 "	4.166	1.600
9 to 10 "	126 "	9.834	2.102
10 to 11 "	142 "	12.241	2.101
11 to 12 "	127 "	11.759	1.778
12 to 1 p.m.	82 "	8.200	0.984

MEADER.

On December 15th, the urine was saved for the entire day, having been kept also through the night previous, from 12.45 a.m. At 5 p.m. of this day the patient ate a hearty tea; from this time she took no food till 11 a.m. December 16th, when we ceased collecting the urine for a few hours.

The same evening (December 16th) the patient ate a bad tea, at 5 p.m., composed of ordinary diet. The urine was collected from 8 p.m. The patient took no food till 12 a.m. next morning (December 17th). Thus she had no food for 18 hours. At 4 p.m. she took dinner and tea together. The urine was now continuously collected (from 8 p.m.); sometimes hourly; at others, during various periods, to 3 a.m. December 21st. December 17th, at 12 p.m., the patient took eight drachms of cane sugar, in 275 c.c. of water. At tea, the previous evening, she drank 570 c.c., and another 180 c.c. at 1 a.m.; beside this, she drank nothing till breakfast, at 9 a.m. the following morning.

December 18th.—At 11 p.m., took a mug of tea and a round and a half of toast.

19th.—At 10 a.m., took eight drachms of sugar of milk in 275 c.c. of water, the patient having taken no food since the tea and toast on the previous evening. On the same day she dined at 4 p.m., on fish, mutton chop, bread, and tea; during the rest of the evening she took nothing but water. At 12 p.m., eight drachms of sugar of milk, in the usual quantity of water, was given her.

20th.—At 3 a.m., she took some bread and butter and tea. Breakfasted at 10. Dined at 4, on a similar diet to that of the day before. 12 p.m., she drank eight drachms of sugar of milk, in 275 c.c. of water.

DECEMBER 14TH.			
Hour.	Quantity.	Sugar.	Urea.
5 to 9.15 p.m.	125 c.c.	2.976	1.975
9.15 to 10.45 p.m.	83 „	1.921	1.045
10.45 to 11.45 „	155 „	3.799	1.813
11.45 to 12.45 a.m.	117 „	3.052	1.240
DECEMBER 15TH.			
12.45 to 9 a.m.	2090 c.c.	96.759	15.048
9 to 2 p.m.	1205 „	37.631	7.230
2 to 12 „	1890 „	98.437	11.340
DECEMBER 16TH.			
12 to 9 a.m.	1025 c.c.	53.385	6.563
9 to 11 „	44 „	2.291	1.410

SUGAR AND UREA IN THE URINE

DECEMBER 16TH AND 17TH.			
Hour.	Total Quantity.	Total Sugar.	Total Urea.
8 to 10 p.m.	503 c.c.	25.150	4.024
10 to 11 „	272 „	12.362	2.067
11 to 1 a.m.	345 „	16.273	3.036
1 to 2 „	210 „	4.687	1.680
2 to 9 „	635 „	23.694	6.350
9 to 11 „	107 „	3.262	1.458
11 to 12 „	30 „	1.041	0.456
12 to 4 p.m.	570 „	29.688	4.104
4 to 9 „	1302 „	70.924	6.786
9 to 12 „	660 „	33.000	3.496
DECEMBER 18TH.			
12 to 1 a.m.	235 c.c.	13.976	1.222
1 to 2 „	282 „	14.100	1.381
2 to 3 „	225 „	10.416	1.125
3 to 9 „	840 „	47.727	5.040
9 to 11 „	217 „	12.616	2.039
11 to 3.30 p.m.	680 „	35.836	3.400
3.30 to 7 p.m.	1200 „	60.000	5.520
7 to 9 p.m.	375 „	20.833	2.875
DECEMBER 19TH.			
9 p.m. to 9 a.m.	2865 c.c.	132.638	18.336
9 to 10 a.m.	107 „	6.079	0.920
10 to 11 „	150 „	8.333	1.120
11 to 12 „	165 „	9.375	1.270
12 to 1 p.m.	102 „	6.071	0.683
1 to 4 „	1035 „	49.759	7.969
4 to 10 „	610 „	31.770	4.026
10 to 12 „	390 „	18.923	2.964
DECEMBER 20TH.			
12 to 1 a.m.	255 c.c.	11.590	1.785
1 to 2 „	230 „	10.865	1.610
2 to 3 „	158 „	8.977	1.216
3 to 5 p.m.	2873 „	149.719	16.683
5 to 7 „	375 „	23.439	1.987
7 to 8 „	305 „	16.576	1.830
8 to 10 „	500 „	24.038	3.100
10 to 12 „	375 „	20.380	2.625
DECEMBER 21ST.			
12 to 1 a.m.	210 c.c.	10.744	1.449
1 to 2 „	234 „	10.833	1.544
2 to 3 „	195 „	9.375	1.267

An intermission then occurred, and the urine was again collected from 9 a.m., December 22d, and kept from this time till 1 p.m., December 24th, over various periods.

December 22d.—She breakfasted at 9; breakfast consisted of bread and butter, with cocoa, with milk and sugar. At 1 p.m. she took eight drachms of glucose, in 275 c.c. of water. Dinner between 4 and 5, consisted of usual food. At 12 p.m. took another eight drachms of glucose, in same amount of water.

23d.—Breakfasted at 9; had three eggs, and tea without milk or sugar, thus solely albuminous food. Dined at 2, good; usual food. Tea at 5; bread and butter; then had nothing till next morning.

24th.—At 9 a.m. drank a mugful of tea; another at 10·20, and then had four eggs. The tea, on both occasions, was without milk or sugar. Dined at 2; usual food.

25th.—Took no starch food on this day, from 6 p.m. (nor milk).

26th.—Breakfasted, at 9·30, on egg and tea, without milk or sugar. Between 1 and 2, had meat solely. At 5 p.m. drank a solution containing three drachms of glucose. At 9 p.m. had meat and a very small piece of bread.

27th.—Breakfasted on eggs and tea, without sugar or milk, at 9·30. Dined, at 1·45, on chop and beef tea solely.

DECEMBER 22D.			
Hour.	Quantity.	Sugar.	Urea.
9 to 11 a.m.	472 c.c.	32·777	3·020
11 to 12	258 „	13·913	1·522
12 to 1 p.m.	55 „	3·197	0·368
1 to 2 „	105 „	11·079	1·092
2 to 3 „	187 „	12·331	0·991
3 to 4 „	130 „	9·027	0·728
4 to 9 „	1217 „	67·611	9·249
9 to 12	760 „	35·183	4·712
DECEMBER 23D.			
12 to 1 a.m.	280 c.c.	12·069	1·820
1 to 3 „	255 „	10·125	3·162
3 to 9 „	145 „	40·277	7·221
9 to 10 „	54 „	2·596	0·540
10 to 11 „	75 „	3·472	0·795
11 to 12	54 „	2·410	0·631
12 to 1 p.m.	87 „	3·625	1·061

DECEMBER 24TH.			
Hour.	Quantity.	Sugar.	Urea.
1 to 9 a.m.	3950 c.c.	154.296	31.235
9 to 10 „	110 „	4.741	1.001
10 to 11 „	135 „	5.443	1.593
11 to 12 „	90 „	3.629	1.116
12 to 1 p.m.	78 „	2.635	0.982

Another intermission then occurred in the urine, which was again collected from 4 p.m. to 8 p.m., December 26th. Then again it was collected from 11 a.m. to 3.30 p.m., December 27th. On this last day the amount of urine was very small, and then the chloride of sodium was allowed for. The amount of sugar also was so small that it was difficult to tell when all trace of blue colour was gone, and some mostly remained.

DECEMBER 26TH.			
Hour.	Total Quantity.	Total Sugar.	Total Urea.
4 to 5 p.m.	120 c.c.	5.769	1.224
5 to 6 „	128 „	6.666	1.190
6 to 7 „	205 „	9.318	1.640
7 to 8 „	154 „	6.875	1.185

DECEMBER 27TH.			
11 a.m. to 1.30 p.m. ...	133 c.c.	3.228	1.436
1.30 to 2.30 p.m.	45 „	0.852	0.567
2.30 to 3.30 „	50 „	0.961	0.700

5. *Temperature.*

Charts are given to show the variation in the temperature each quarter of an hour, judged of by a thermometer placed in the axilla. In the columns above, the amount of sugar, urea, chloride of sodium, and water, is given hourly, and written down opposite to the time at which the urine was collected. The hourly amount is always given.

HUDSON.

October 24th.—The patient finished dinner at 1.10. He ate heartily of fish, bread, and potatoes, and took half a pint of porter. He took nothing more till tea, which he completed by 6.45, and ate heartily of meat and bread and butter; after this he took nothing till after 10 p.m.

26th.—Breakfasted exactly at 9; ate very heartily. At 4 a.m., previous, he had taken some tea and a little bread and butter.

27th.—He commenced his breakfast at 7; it consisted of tea and toast, the tea with milk and sugar; breakfast very good.

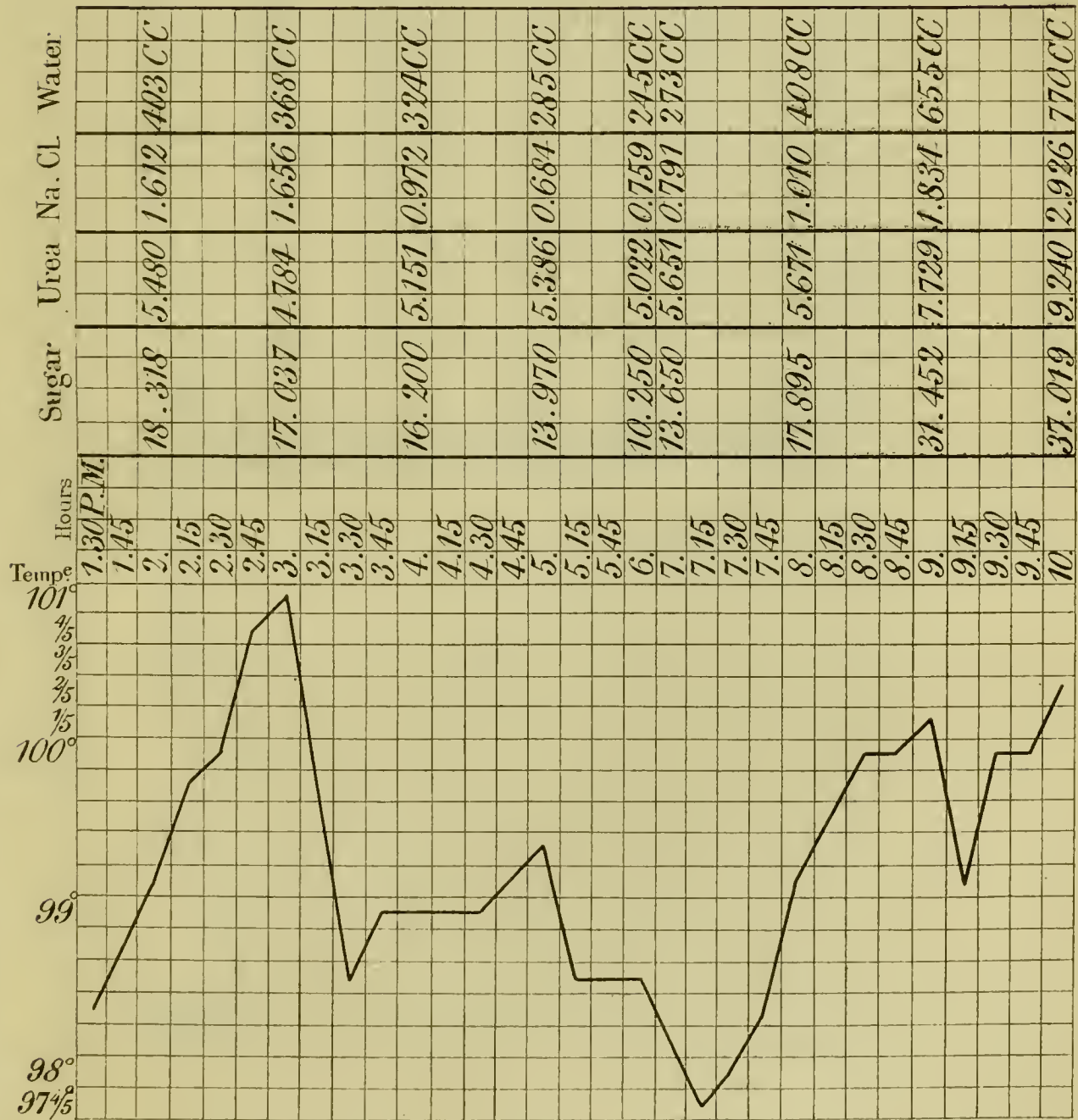
28th.—Breakfasted at 7.30; he ate six eggs for breakfast, and less bread than usual. Dined, at 1, on meat, bread, and potatoes, and half a pint of beer; he ate heartily. Tea at 5, very good.

At 6 p.m. the temperature rose suddenly to $100\frac{4}{5}^{\circ}$, and, in a few minutes, fell again to $99\frac{1}{5}^{\circ}$. The rise followed after a cup of tea, by no means hot. A similar rapid rise, and subsequent fall, after drinking, was noticed on another occasion.

These charts require no remarks, as they speak for themselves. Suffice it to say, that the temperature of the axilla was taken by an accurate thermometer, graduated into fifths.

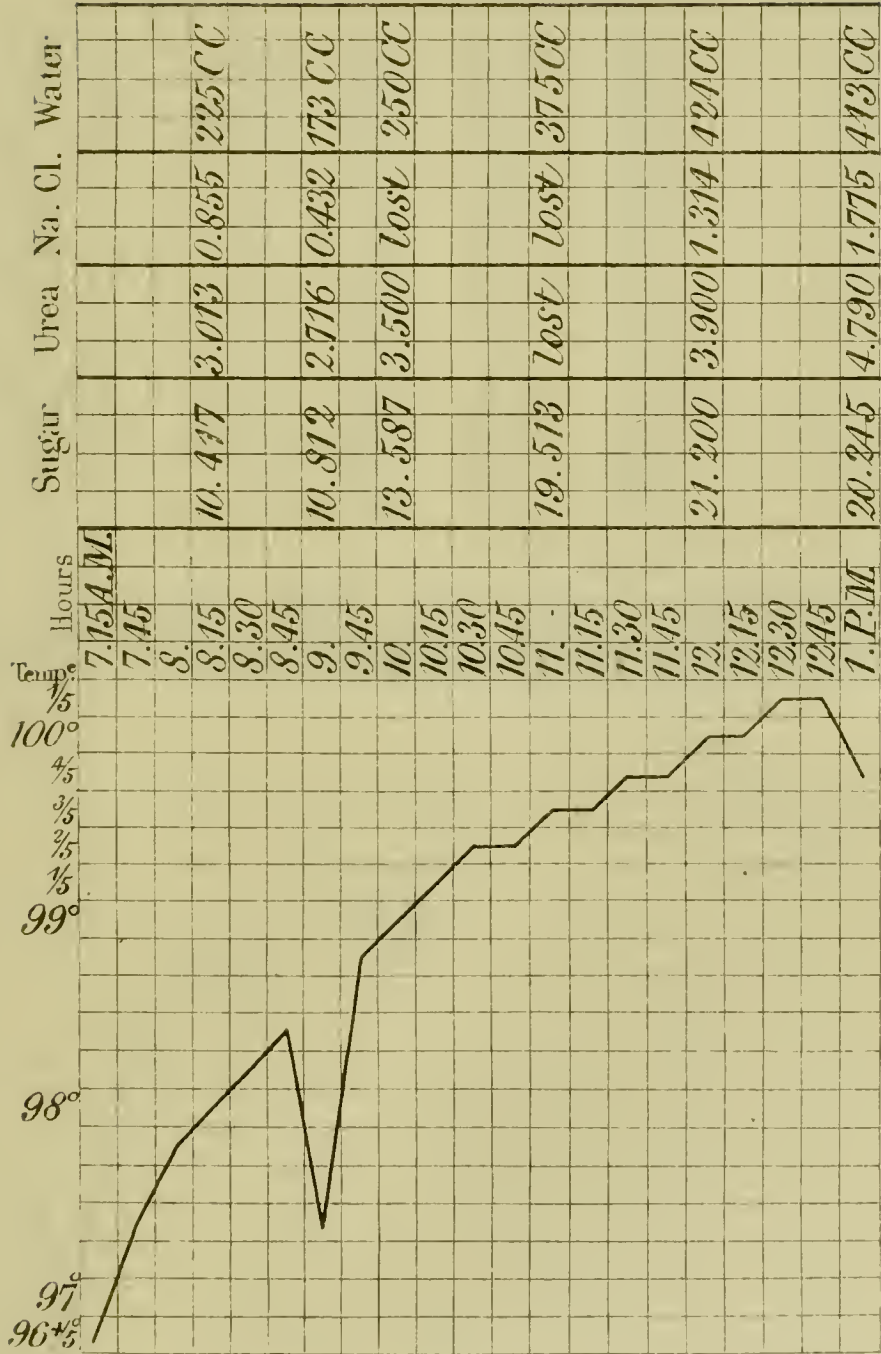
TEMPERATURE IN DIABETES MELLITUS.

OCTOBER 24TH



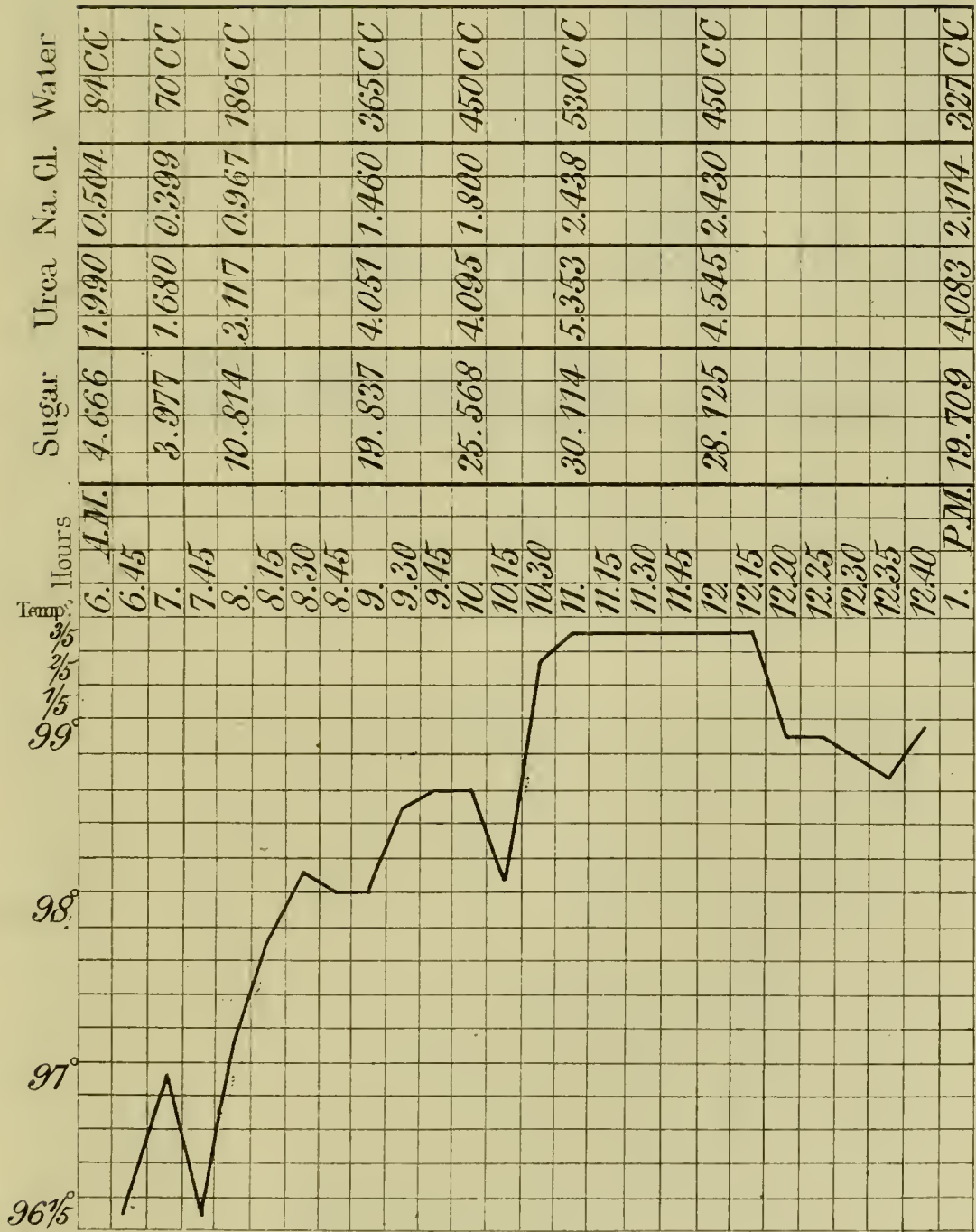


OCTOBER 26TH



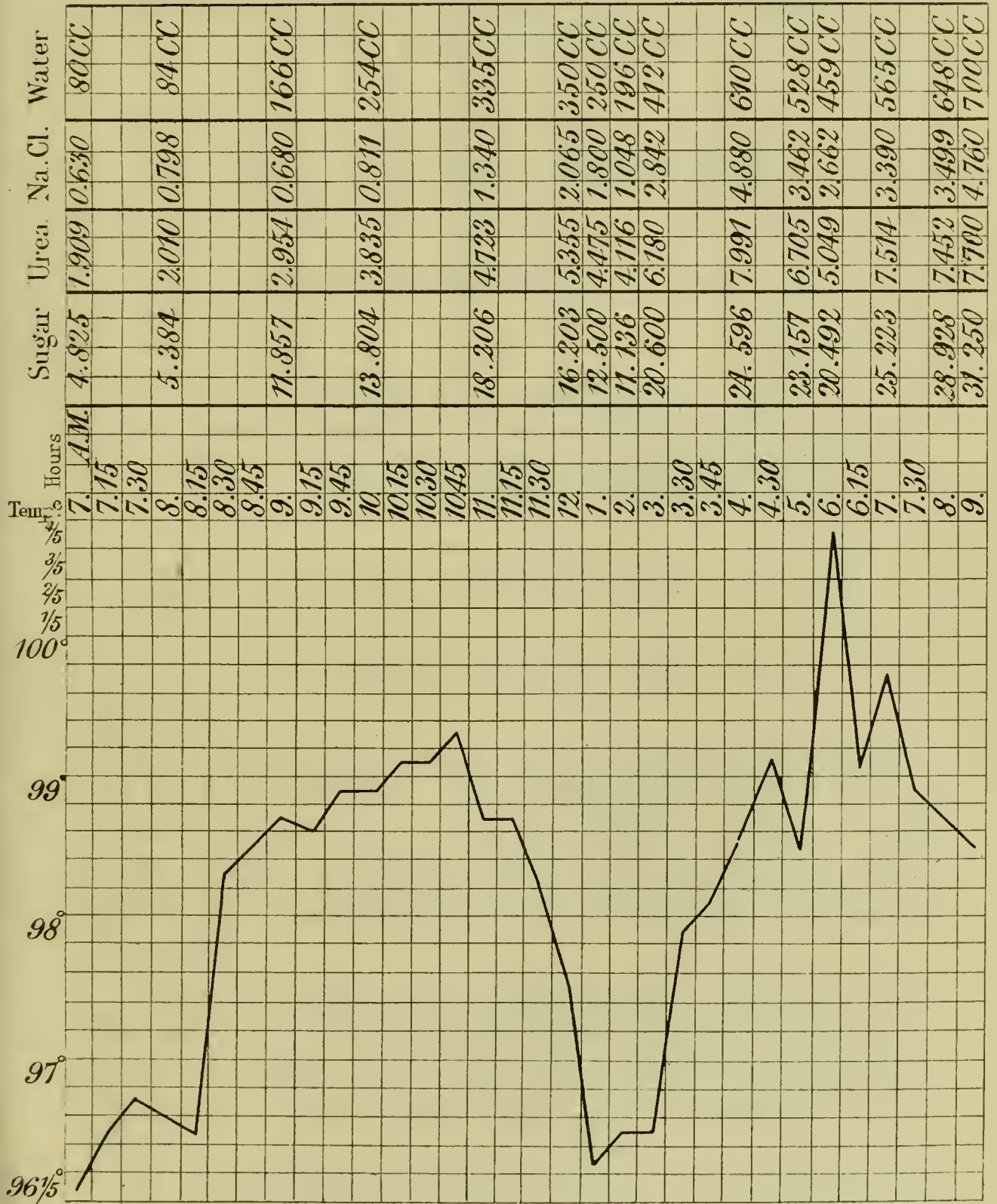
W. West, lith.

OCTOBER 27TH



W. West, Lith.

OCTOBER 28TH



W. West, lch.

ON THE
TEMPERATURE, UREA, CHLORIDE OF SODIUM,
AND URINARY WATER

IN
SCARLET FEVER;

AND ON A
CYCLE IN DISEASE AND HEALTH.

BY
SYDNEY RINGER, M.B.,
RESIDENT MEDICAL OFFICER TO UNIVERSITY COLLEGE HOSPITAL; AND LATE
MEDICAL REGISTRAR TO THE HOSPITAL FOR SICK CHILDREN,
GREAT ORMOND STREET, LONDON.

COMMUNICATED BY
DR. GARROD, F.R.S.

Received Jan. 4th.—Read Jan 28th, 1862.

THESE observations were made on inmates of the Hospital for Sick Children. The patients were under the care of Dr. West, Dr. Jenner, and Dr. Hillier. I beg to avail myself of this opportunity of thanking these gentlemen for affording me every facility in the prosecution of these investigations.

These experiments were undertaken to ascertain what relationship exists between the urinary excreta and the temperature in scarlet fever; and this paper is intended to be a sequel of my former paper on 'Ague' published by this Society.

The temperature is given in charts. The variations of each day are separated from each other by a red line, and

at the head of the column thus formed the day of the disease is given.

Above the temperature, five columns are given ; the first, gives the hour of the day ; second, gives the day of the month ; third, the daily amount of urea ; fourth, the daily amount of chloride of sodium ; fifth, the daily amount of urinary water. The urea and chloride of sodium are given in grammes ; the urinary water in cubic centimetres.

The urine was analysed daily ; and the amounts of the different constituents for twenty-four hours are put down on the day on which the urine was collected, and therefore belong to the previous day ; thus, when subsequently I refer to the urine of any day, I of course mean the urine collected on the morning of the following day.

The urea and chloride of sodium were analysed by Liebig's volumetric method. The chloride of sodium was not got rid of, but the usual allowance was made in estimating the quantity of urea.

The following are the subjects treated of :—1st. The temperature and its relationship to the urinary excreta. 2nd. The urea. 3rd. The chlorides. 4th. The urinary water. 5th. The albumen in the urine. 6th. The blood in the urine. 7th. A cycle in disease. 8th. A cycle in health, and its relation to the cycle in disease.

On the temperature in scarlet fever.

The duration of the elevation of the temperature varies ; thus, in seven cases it fell on the fifth day of the disease, in four cases on the tenth day, in two cases on the fifteenth day, in one case on the twentieth day, in two cases on the fourth day, in one case on the sixth day, and in two other cases the temperature fell so gradually, that it was impossible to say exactly on which day it reached its normal point.

It thus appears that in the large majority of cases the temperature falls on the fifth, tenth, fifteenth, or twentieth day, that is either on the fifth or a multiple of the fifth day of the disease ; so constant indeed is this, that if the

temperature should remain high on the fifth, tenth, or fifteenth day, we may look forward to a continuation of the fever for another five days. Further, in those cases in which the temperature continues high till the tenth, fifteenth, or twentieth day, it generally experiences a depression on the fifth day preceding its complete fall; for instance, if the temperature falls permanently on the fifteenth day, there generally occurs a depression of variable amount on the fifth and tenth days.

After each of these falls the temperature may rise again, reaching a point during the second five days, as high as, or higher than it did during the first five days, as in Cases 8, 17, 18, and 22. In other cases, after the fall on the fifth day, the temperature remains at this point till the following tenth day, on which day it experiences another abrupt fall, or it may gradually decline, passing almost imperceptibly into the normal temperature, reaching this point on the tenth day, as in Cases 5, 7, 16, 8.

Each of these falls in the temperature is accompanied by an improvement in the state of the patient, which is always in proportion to the extent of the fall. If the temperature again rises, the patient again relapses, but if it remains at the point it reached at its first fall the improvement is permanent.

The temperature does not usually attain the same height daily during each of the five days, but the point reached gradually increases during the second and third days, and then falls again towards the fifth; in some cases, however, it goes on increasing till the fourth day, and then experiences an abrupt fall on the fifth. It thus appears that the temperature (*i. e.* the fever) forms arcs or cycles, lasting over a period of five days. The height the temperature attained varied greatly in different cases; in some the elevation was just appreciable, in others it reached 105° Fahr.

Of seventeen cases that came early under notice, the average maximum temperature was a little over 103°. As might be expected, the temperature reached a higher point in the cases of long duration.

In some cases the highest elevation was attained on the first day, but in the severer cases it generally reached its highest point on the second or third, and perhaps not till the sixth or even the eleventh day.

Subsequent to the great fall experienced on the fifth, tenth, or fifteenth day, the temperature often remained over a variable period rather too high, the period being in some cases fourteen or fifteen days; the degree of elevation also varied, in some cases (Case 1) being between 100° and 101° , but more frequently between 99° and 100° . This slighter elevation of the temperature in most cases formed cycles of five days, as in Cases 2, 6, 10, and 11. In Case 11 this occurred after the second elevation on the twenty-sixth day.¹

This slight subsequent elevation of the temperature, if of any persistence, is coincident with a continuance of the lesions produced by the scarlet fever; as, for instance, of the sore throat, or of the enlargement of the gland, or from discharge from the ears, &c.

There is no connection between the duration of the primary high temperature and the subsequent slighter one; thus, it can be seen (Case 1) that in some cases, where the great fall in the temperature occurred on the fifth day, a long subsequent slight elevation occurred; it must, therefore, have depended on the constitutional state of the patient. It certainly sometimes precedes Bright's disease.

At a variable period after the scarlet fever, a subsequent high rise in the temperature not unfrequently occurred, due to intercurrent disease. In many cases the nature of the intercurrent disease was determined, in other cases nothing capable of causing the elevation of the temperature could be discovered.

The day of the disease (counting from the commencement of the scarlet fever) varied. In the cases of albuminuria

¹ It must be borne in mind that in counting the second cycle of five days we must not take in the day of the fall, as this belongs to the previous cycle, but must begin to count from the day after this.

it began on the seventh, nineteenth, twentieth, twenty-third, twenty-ninth, and thirty-third days.

In those cases in which the elevation was probably due to heart disease, it began on the eighth day. In those cases in which the cause could not be determined, it began in one case on the eighth and in the other on the tenth. In one case of urticaria and chicken-pox it began on the sixth day. In a case of tuberculosis, on the ninth. The degree of the elevation of the temperature varied thus :

4 cases ranged between	102° and 103°
3 " "	103° and 104°
4 " "	104° and 105°
1 case it was	105 $\frac{1}{5}$ °.

The duration of the elevation varied ; thus, in—

2 cases the temperature fell on the	second day.
1 case " "	fourth day.
3 cases " "	fifth day.
1 case " "	sixth day.
1 " " "	tenth day.
1 " " "	eleventh day.
1 " " "	thirteenth day.

The cause of the elevation also varied.

In 6 cases it was due to	albuminuria.
In 1 case " "	tuberculosis.
In 1 " " "	chicken-pox.
In 2 cases " "	heart disease.
In 2 " it was	uncertain.

On examining the previous cases, it will be seen that the rise in the temperature due to an intercurrent disease either fell on the fifth day from the commencement of its rise, or on the fifth day from the commencement of the scarlet fever ; that is to say, the secondary rise in some cases adopts the cycle existing previously, or checks this and determines another.

Thus, in Case 1 the elevation lasted five days, and fell on

the twenty-seventh day of the disease, counting from the commencement of the scarlet fever.

In Case 17 the elevation fell on the fifth and tenth days from its own commencement, and as it began on the sixth day of the scarlet fever, it fell on the fifteenth day of that disease.

In Case 19 the secondary elevation fell on the fifth day from its own commencement.

In Case 22 it fell on the fifth, tenth, and twentieth days from its own commencement, and on the twelfth, seventeenth, and twenty-seventh of the scarlet fever. In this case I have counted the second rise from the eighth day, the two previous days being part of a previous cycle of the scarlet fever.

In the following cases the elevation caused by the intercurrent disease lasted a variable number of days, but fell on the fifth day, counting from the commencement of the scarlet fever.

Case 6.—It fell on the fourth day from its own commencement, on the tenth from the commencement of the scarlet fever.

Case 12.—It fell on the second day from its own commencement, on the twentieth from the commencement of the scarlet fever.

Case 20.—It fell on the thirteenth day from its own commencement; on the twentieth from the commencement of the scarlet fever.

In this case I have considered the second rise due to the intercurrent disease; to begin on the eighth day, and the two previous days to belong to the previous cycle of the scarlet fever.

Case 25.—It fell on the second day from its own commencement; on the twentieth from the commencement of the scarlet fever.

Case 26.—It fell on the sixth day from its own commencement; on the fifteenth, and again on the twentieth, from the commencement of the scarlet fever.

It is thus seen that the subsequent rise in the temperature

due to intercurrent inflammations, &c., strictly follow out the cyclical law, only one exception occurring; this was Case 23, in which the temperature fell on the sixth day from the commencement of the secondary rise, and on the thirteenth day from the commencement of the scarlet fever.

Sometimes after the fever had declined a sudden slight elevation occurred, limited to one day, and often to a few hours of the day, the patient being next day in the usual health and the temperature normal.

In 1 case it rose to $102\frac{2}{5}$ on the twenty-fifth day,	} Counting from the commence- ment of the scarlet fever.
In 1 „ „ $100\frac{1}{5}$ „ fifteenth day,	
In 1 „ „ 101 „ eleventh day,	

On the daily variations of the temperature.—In some cases the temperature remained at much the same height throughout the day; in other cases it fell a variable amount in the morning, and again rose during the day, forming a daily arc or cycle. The former generally occurred in the severer cases and at the commencement of the disease, and the latter at the termination, and may be taken as a sign of improvement. The time of the day at which the temperature reached its highest point varied between 9 a.m. and 11 p.m.; from 2 to 8 appears to be the most frequent hours. Two patients died from the immediate effects of the fever; one died on the fourth day of the disease; one died on the eighth day of the disease.

On the urea.

From the above cases it appears that the quantity of urea undergoes no increase with the elevation of the temperature, that is, during the fever days. If, indeed, we accept .800 grms. of urea per kilogramme of weight as the amount normal per diem in children, it often suffered a great diminution.

It may, however, be objected that this is too high; and, secondly, that in many of the previous cases the urea falls

with the decline of the temperature, and that this shows that it had previously undergone an increase.

It may be fairly assumed, I think, that the amount of urea voided by these patients during the last ten or fifteen days of their residence in the hospital was not in excess of the quantity in health, especially where the examination extended over a long period (thirty or forty days), at which time the quantity of urea could not have been affected by any previous retention during the fever. Indeed, it appears to me that, leading a quiet, hospital life, and often spending the time in bed, that this amount is too low; but even accepting this amount as normal to the patient, on no occasion was the quantity of the urea increased during the elevation of the temperature; often, indeed, it was below it. This is shown in the following table, in which I have first given the daily average amount of urea per kilogramme of the fever days, and that of several of the last days during which the analyses were made.

Case 3.	From the second to the fourth day inclusive	. 0.477
„	„ tenth to the twenty-eighth day inclusive	0.687
Case 4.	„ sixth to the ninth day inclusive	. 0.527
„	„ nineteenth to the thirty-second day inclus.	0.706
Case 10.	„ second to the third day inclusive	. 0.569
„	„ twelfth to the twenty-seventh day inclus.	0.642
Case 18.	„ second to the thirteenth day inclusive	. 0.552
„	„ twentieth to the thirty-first day inclusive	0.634
Case 20.	„ tenth to the twelfth days inclusive	. 0.561
„	„ twentieth to the thirty-sixth day inclusive	0.551

That the subsequent decrease in the amount of the urea is not due to the decline of the temperature is seen in some cases, as the 18th and 20th, in which the urea falls about the same time as in the other cases, in spite of a continuation of the elevation of the temperature, as the temperature in these cases continued high a long time after the decline of the urea; this disassociation of the urea and the temperature plainly shows that the decrease in the amount of the urea is independent of the temperature, and therefore their occa-

sionally occurring at the same time in no way shows that there was an increased elimination during the fever.

After the first few days the urea invariably falls, reaching point often considerably below the normal amount; thus, in—

Case 1.	The average daily amount per kilogramme, from the sixth to the fourteenth day inclusive, was .	0·417
„	The normal amount was .	0·642
Case 3.	The average daily amount per kilogramme, from the sixth to the ninth day inclusive, was .	0·400
„	The normal amount was .	0·687
Case 4.	The average daily amount per kilogramme, from the eighth to the fourteenth day inclusive, was .	0·422
„	The normal amount was .	0·706
Case 10.	The average daily amount per kilogramme from the fourth to the eleventh day inclusive, was .	0·457
„	The normal amount was .	0·642
Case 18.	The average daily amount per kilogramme, from the fifth to the sixth day inclusive, was .	0·439
„	The normal amount was .	0·634
Case 20.	The average daily amount per kilogramme, from the tenth to the nineteenth day inclusive, was .	0·417
„	The normal amount was .	0·551

A diminution of this kind usually occurs after the subsidence of fevers, due probably to the appetite not being completely restored, and also to the food being more thoroughly assimilated and tissue change not being so active.

But in these cases of scarlet fever the above explanation will not, I think, hold; for, first, the diminution in the urea usually lasts only over a few days after other fevers, whilst in these cases it often remained for many. Secondly, we have previously seen that there is no increase in the amount of the urea coincident with the increase in the temperature, and thus, probably, there is retention in the system, either of urea or some product capable of producing urea. In similar cases of retention in typhoid fever we have a subsequent increase in the amount of the urea, instead of the diminution. Thirdly, it has been before stated that the great diminution occurs quite independently

of the temperature, sometimes even when the temperature for several days remains at even 103° .

Thus I have tried to show that—First, there is no increase in the amount of urea during the fever. Second, that, subsequent to the fever, there is a great diminution of the urea, &c. Third, that this diminution cannot be explained in the usual manner. May the following be the explanation—namely, that the contagion has a similar action on the kidneys to that on the skin, tongue, and fauces, for we find in the urine epithelium from the bladder, pelvis of the kidney, and from the kidney itself, during the fever days. It may be objected that the impaired functional activity of the kidneys lasts longer than the rash, but the organs involved do not at once recover their normal condition on the disappearance of the rash, as is seen in the case of the tongue and fauces.

In most of the cases, especially where the convalescence was slow, the children became puffy about the face, there being, however, no pitting on pressure; this occurred without the appearance of albumen or blood in the urine; perhaps this may be accounted for by the retention of urea in these cases being unusually marked.

On the occurrence of acute Bright's disease after the fever the urea was variously affected; in some cases it was greatly diminished in quantity.

Case 1.—The temperature rose on the twenty-third day to $102\frac{2}{5}^{\circ}$, and then gradually fell during the following three days; on the fifth day it was normal again. Daily average amount per kilogramme, from the sixth to the twenty-first days inclusive, 0.464. During the following four fever (inflammatory) days, 0.373. The urea immediately regained its full quantity; thus, from the twenty-seventh to the thirty-fifth it was, per kilogramme, 0.641.

In the above case the albumen never amounted to more than a mere trace, and thus, probably, did not, to an appreciable degree, interfere with the quantitative analysis; the albumen lasted only during the five days of elevation of temperature, and hence, if it had any effect on the analysis,

it must be to give too great an amount of urea, and thus the diminution in the amount of urea will be greater than that given.

Case 12.—In this case, on the occurrence of the inflammation, blood (with a very large amount of albumen) was found in the urine; the albumen was removed by animal charcoal. The rise in the temperature occurred on the nineteenth day (105); on the following day it fell to 99 again. From the eighth to the eighteenth days inclusive, average daily amount of urea was 9·185. On the twenty-second day it was 1·875; on the twenty-third day it was 0·510.

I have given the total amount above, not the quantity per kilogramme, as they are so small during the above two days.

Case 24.—The urea was estimated quantitatively only till the twelfth day; after this it was discontinued till the sixty-third day, but, during the time, the patient had a severe attack of Bright's disease, with much blood and a large amount of albumen. On the fiftieth day she was much improved, on the sixty-first there was scarcely any anasarca, and from the sixty-third to the sixty-eighth the merest trace of albumen in the urine. Average daily amount of urea, per kilogramme, from the fifth to the twelfth days inclusive, 0·582. Average daily amount of urea per kilogramme, from the sixty-third to the sixty-eighth days inclusive, 0·268.

The last case not only shows how large the diminution often is, but that it may continue over a very long period, and long after active disease in the kidney has ceased.

Case 25.—Observations were made for eight days; on each day there was a variable amount of albumen, which was removed by animal charcoal; the temperature on three occasions rose gradually, over a space of three days, from normal to 105; the urea showed no corresponding increase on these days. The average daily amount for the eight days was only 10·241 grains. His weight was not taken, but assum-

ing 26 kilogrammes, for each kilogramme there was 0·093 grms.

In other cases no diminution occurred on the occurrence of the inflammation; thus, Case 25, on the twenty-ninth day, Bright's disease supervened, judging by the sudden elevation of the temperature, and the appearance of albumen and blood in the urine, yet, notwithstanding, the amount of urea continued as it was before or very nearly so. Thus, from the sixteenth to the twenty-eighth days inclusive, the average daily amount per kilogramme was 0·523 grms. From the twenty-ninth to the thirty-fourth inclusive it was 0·488 grms.

On the chlorides.

The chlorides were never absent from the urine that was analysed; the quantity, however, was always much diminished during the fever days; thus, in—

Case 3, the daily average amount per kilogramme, from the second to the fourth day, was	.	.	.	0·032
Case 10, the daily average amount per kilogramme, from the second to the fourth day, was	.	.	.	0·054
Case 20, the daily average amount per kilogramme, from the first to the fourteenth day, was	.	.	.	0·080
Case 24, the daily average amount per kilogramme, from the fifth to the twelfth day, was	.	.	.	0·093

During the three or four days following the fever the quantity of chloride increased gradually; thus, in

Case 3, the average daily amount per kilogramme, from the fifth to the eleventh day, was	.	.	.	0·093
Case 10, the average daily amount per kilogramme, from the fifth to the eleventh day, was	.	.	.	0·125

After this they became normal in quantity; thus, in

Case 3, the average daily amount per kilogramme, from the tenth to the twenty-fifth day, was	.	.	.	0·210
Case 10, the average daily amount per kilogramme, from the thirteenth to the twenty-seventh day, was	.	.	.	0·228

In one case of Bright's disease the chlorides suffered scarcely any diminution in their quantity during the fever days; thus, in Case 1—

Average daily amount per kilogramme, from the twenty-third to the twenty-sixth day (fever days)	0·110
Average daily amount per kilogramme, from the twenty-seventh to the thirty-fourth day (non-fever days)	0·134

It still remains doubtful whether the chlorides are eliminated as a secretion, or merely as a solution in the urinary water; if it be secreted by the kidney through any diminution in the secretive power of the kidney, it should show itself in a diminution of the amount of the chloride of sodium.

In the case given above there was a decided diminution in the amount of urea during the fever days of Bright's disease, and this, I have attempted to show, was due to diminution in the secretive power of the kidney. But in this case the chloride of sodium was scarcely diminished; thus, this single case would go to show that the urea passes out in the form of a solution. The close relationship also between the amount of chloride and the urinary water tends to prove the same conclusion.

On the urinary water.

During the fever days the amount of urinary water varies very greatly; thus, in—

Case 10, the average daily amount per kilogramme was	11	c.c.
„ 3,	„	12 „
„ 4,	„	18 „
„ 20,	„	20·2 „
„ 18,	„	35·3 „
„ 24,	„	66 „

During the subsequent non-fever days the amount also varied somewhat; thus, in—

Case 2, the average daily amount per kilogramme was 17 c.c.			
„ 18,	„	„	22 „
„ 24,	„	„	23 „
„ 3,	„	„	25·9 „
„ 4,	„	„	26 „
„ 10,	„	„	28·4 „
„ 20,	„	„	27·6 „
„ 25,	„	„	29·4 „

These last quantities may, I think, be taken as the amount usual per kilogramme in children; this gives an average of 24·6. I am aware this is much below the amount usually received; thus, Dr. Parkes¹ gives 59 c.c. The above quantity agrees very closely to the amount given by Dr. Parkes per kilogramme in adults.

If this assumption be correct, it follows that often, during the fever days, there is no decline in the amount of urinary water, and in some cases there is a very large excess.

On the albumen in the urine.

The albumen appears at two different periods; first, during the fever, and second, later—about the third week—at which time it is often much larger in quantity, longer in its duration, and accompanied by a second elevation of the temperature.

1st. Its appearance during the fever days, out of twenty-one cases in which the urine was examined.—In only one did any albumen occur; it was slight in amount, and was present on the fifth and sixth days. It must be borne in mind, however, that in many of these cases several of the fever days had elapsed before their admission.

2nd. Its appearance during convalescence of eighteen patients who were in the hospital for a considerable time.—Seven had albumen during the period; three other cases are given; these were admitted with albuminuria.

¹ 'On Urine,' p. 44.

The time of its appearance varied ; thus —

In Case 6 it appeared on the ninth day.

- | | | |
|------------|---|-------------------|
| „ 25 | „ | eighteenth day. |
| „ 12 | „ | twentieth day. |
| „ 1 and 19 | „ | twenty-third day. |
| „ 11 | it first appeared on the eleventh day, but after a day
or two it discontinued, and reappeared on the
twentieth. | |

The duration of the albuminuria varied ; thus in—

Case 1, it lasted three days.

- | | | |
|-------|---|------------------------------|
| „ 6, | „ | eleven days. |
| „ 25, | „ | twenty days. |
| „ 11, | „ | more than twenty-seven days. |
| „ 19, | „ | forty-three days. |
| „ 12, | „ | forty-nine days. |

Taking the elevation of the temperature as a test of the severity of the inflammation, it is seen that there is no necessary connection between the intensity and duration of the inflammation and the duration of the albumen in the urine. This can be seen by comparing the following table with the one above :

Case 1, the temperature reached 102, and lasted four days.

- | | | | | |
|-------|---|--------------------|---|-------------|
| „ 6, | „ | 103, | „ | three days. |
| „ 25, | „ | 104, | „ | one day. |
| „ 19, | „ | 102 ² , | „ | four days. |
| „ 12, | „ | 105, | „ | one day. |

Moreover, there is no necessary relationship between the temperature and the amount of the albumen. This can be seen by comparing the following table with the one above :

Case 1, very slight trace.

- | | |
|-------|----------------------|
| „ 6, | an enormous amount. |
| „ 25, | very slight trace. |
| „ 19, | very large quantity. |
| „ 12, | a large quantity. |

The albumen appears in the urine very soon after the elevation of the temperature ; thus, in —

Case 1, the temperature rose on the twenty-third day ; albumen appeared on the twenty-third day.

Case 6, the temperature rose on the seventh day ; albumen appeared on the ninth day.

Case 11, the temperature rose on the eleventh day ; albumen appeared on the eleventh day.

Case 12, the temperature rose on the nineteenth day ; albumen appeared on the twentieth day.

On blood in the urine.

Relationship between the elevation of the temperature and the appearance of blood in the urine :

1st. No blood may follow the rise of the temperature. Case 1, there was no blood. Case 6, never smoky ; urine not examined microscopically.

2nd. In those cases in which blood appeared its appearance was always preceded by a rise in the temperature. Case 11, temperature rose on the twentieth day ; blood appeared on the twenty-first. Case 12, temperature rose on the nineteenth day ; blood appeared on the twentieth. Case 25, temperature rose on the twenty-ninth day ; blood appeared on the twenty-ninth.

The blood in some cases continued long after the decline of the temperature ; thus, the continuance of blood cannot be taken as evidence of a continuation of the inflammatory action of the kidney ; thus, in Case 11, the temperature fell on the twenty-seventh ; the blood continued in the urine till the thirty-seventh day. Case 12, the temperature fell on the twentieth ; the blood continued in the urine till the twenty-first day. Case 19, the temperature fell on the thirty-seventh ; the urine contained blood till after the sixty-fifth day. Case 25, the temperature fell on the thirtieth day ; the urine contained blood till the forty-first day.

Relationship between the blood and the amount of albumen in the urine.

1st. A very large amount of albumen may occur in the urine without any blood, as in Case 6.

2nd. Blood, even to a large amount, may exist with the slightest trace of albumen; and if the blood-corpuscles be allowed to settle to the bottom of the vessel, the supernatant fluid may give no evidence of any albumen by heat and nitric acid, as in Cases 25 and 30.

The cases given were seldom dropsical to the extent of pitting; they, however, often looked puffy in the face. Seven cases gave no pitting on pressure; one case very slight; one case the body pitted deeply on pressure.

In some cases the second elevation of the temperature was followed by a puffiness.

In one case the patient was puffy about the face, without any elevation of the temperature or other evidence of Bright's disease.

In some cases the puffiness about the face preceded the rise of the temperature one or two days. In other cases the rise in the temperature preceded the puffiness¹ for a variable number of days; thus, in Case 6, six days; Case 11, three days; Case 12, one day.

On a cycle in disease.

In these cases it appears that the temperature does not run an equable course, neither remaining at the same temperature throughout, nor observing a period of elevation and decline, but forms arcs or cycles composed of a variable number of days, each cycle, however, being composed of the same number of days in the same patient.

We see from the cases given that no number of days

¹ When I use the term puffy, there was no pitting of the body on pressure.

composing the cycle is peculiar to any disease, but that five days is the most common in all.

In rare cases, in the same patient the number of days composing the cycle may change.

For a further account of the cycle in disease, I must refer to the account given of the temperature.

On a cycle in health.

We have seen that in fevers the temperature forms cycles, and as the variations in the temperature are due to the variations in the amount of tissue change, it follows that we must have a cycle of tissue change. Does such a cycle exist in health? I think it probable, and that this determines the cycles in fever, and not the disease itself, for—

1st. In the same disease the cycle may be composed of a different number of days, the cycle, however, remaining constant in the same patient. If the disease determined the cycle, we should expect it to be composed of the same number of days in all patients, whilst we can readily conceive different people to have a different cycle.

2nd. Different diseases (as scarlet fever, followed by Bright's disease, heart disease, chicken-pox, &c.), occurring in the same patient, adopt the same cycle.

3rd. Not unfrequently after the decline or during the decline of the scarlet fever a second elevation of the temperature occurred, due to some intercurrent disease. This second elevation of the temperature lasted over a very variable number of days, but, with one exception, it fell on either a fifth day from its own commencement or on a fifth day from the commencement of the scarlet fever.

In the latter case the intercurrent elevation of temperature, if of some duration, forms cycles, the first of which cycles only is irregular, the subsequent ones being composed each of five days. If the intercurrent inflammation determined the cycle, we should have expected its first cycle to have lasted five days also, instead of which it appears to adopt a previously existing one; but having commenced in

the middle, it is composed of a shorter number of days. This will be more clearly shown by a typical case.

A case of scarlet fever in which the temperature forms cycles of five days, having again fallen to the normal temperature, is followed on the twenty-second day by another elevation, due to intercurrent disease; this experiences a fall on the twenty-fifth, thirtieth, thirty-fifth, and fortieth days from the commencement of the scarlet fever. The three last cycles of the intercurrent disease being each composed of five days, shows that the normal cycle is one of five days, and that the one which immediately preceded them, composed of only four days, is irregular, but only with regard to its commencement, as its fall takes place on a fifth day from the beginning of the scarlet fever.

The previous elevation of temperature of the scarlet fever affords data from which we can calculate the subsequent cycles, and the intercurrent inflammation corresponds exactly with these, with the exception of the elevation of temperature of the imperfect cycle, which begins in the middle of one, showing that diseases adopt previously existing cycles. In the other case, in which the intercurrent inflammation falls on the fifth day from its own, and not from the fifth day from that of the scarlet fever, it is probable that the intercurrent disease cuts short the immediately preceding cycle, but another one commencing it adopts this.

It may, however, be said that this cyclical condition preceding and influencing any subsequent inflammation was established by the preceding scarlet fever; this I think improbable, for the following reasons:

(A) If the disease determines its cycle, it appears difficult to me to conceive that it should be amenable to the influence of a previous disease, whilst it is readily explained by the supposition that both are influenced by a cycle existing in health.

(B) It is difficult to conceive how the scarlet fever should affect the cycle of a subsequent intercurrent disease, occurring

as it sometimes did, so many days afterwards, in some cases the subsequent elevation not occurring till the thirtieth day.

(c) In a case of pneumonia, the temperature of which I took, the first cycle was composed of six days ; this was followed by a cycle of ten days (two five days' cycles) and by a five days' cycle. This is a case similar to those occurring after Bright's disease, in which the elevation began probably in the middle of a cycle ; but in this case there was no preceding fever to give rise to a cycle which could modify the subsequent elevation, and as it began probably in the middle of a cycle, of course this implies its previous existence, that is, in a state of health.

It may be said this cyclical variation in health can be at once put to the test by taking the temperature in health, and seeing if any such variation exists. But in speaking of cyclical changes of tissue, I mean nitrogenous tissues solely, of which the temperature in fevers is the exponent ; for in fevers probably the hydrocarbons are not at all attacked, for it is said the amount of carbonic acid is not increased, and I have attempted to show in a previous paper that in ague the temperature holds the closest correspondence to the amount of urea excreted, that is, to the amount of nitrogenous matter consumed.

But in health the temperature is largely derived from the combustion of the hydrocarbons of the body, and thus it cannot be taken as a guide to the change occurring in the nitrogenous tissues ; indeed, in health it is probable that the hydrocarbons and the nitrogenous tissues are reciprocal.

Dr. Parkes tells me he has noticed that the urea in Bischoff's and Voet's experiments observed cyclical variations.

Thus, I think it probable that in health we have cycles of tissue (nitrogenous) changes, and in fevers we have the same greatly increased. But if this correspondence holds good between the cycle of health and disease, it is probable that it holds as to the constituent parts of the cycle ; and if so, we have a daily cycle in health corresponding to that in fevers, but of a less degree.

If the above views be correct, it follows that in fevers we have but an increase of the normal tissue change, amenable to the ordinary laws of health.

On the temperature in fevers.

On looking over the cases given, it will be seen that in some the temperature remains almost permanent at an elevated point ; in others there are daily elevations and falls of variable intensity ; the persistence of the elevation of the temperature occurs during the most severe period of the fever ; as it improves, the highest point the temperature reaches may remain the same, but the daily fall increases, this being often the earliest indication of improvement. This has been already noticed in typhoid, but it also holds good in scarlet fever, but to a less degree, partly owing to the fever throughout its course being severe, not having a period of slow increase and decline ; however, even under these circumstances, it is not so marked as in typhoid fever.

The manner in which the temperature becomes persistent during the more severe time of the fever appears to me to be the following.

There is originally a daily rise, or perhaps it is limited to a part of a day ; but as the fever increases in severity, not only does the extreme elevation of the temperature increase, but also the duration of the daily fit ; indeed, after the temperature has attained a variable height, it ceases to rise higher, but the duration of the rise continues to increase.

Thus, suppose it possible to isolate a distinct fit, consisting of the rise and fall of the temperature, in a severe case the temperature, not having had sufficient time to reach its normal point on one day, would encroach on the following ; but there occurring another rise on the second day, before the previous rise has had time to complete its fall, the temperature of the two days coalesce at a certain point, and the longer the duration of the separate fits the higher will be the point at which they will coalesce. These steps are best followed in typhoid fever, in which, at the commence-

ment and decline of the fever, we often have a complete daily fit, in some cases rising from the normal temperature to 105° , and again falling to the normal temperature; this may be repeated for several days;¹ as however, the fever increases in severity the daily falls in the temperature diminish till the fever becomes almost persistent in severity.

The same occurs also in miasmatic fevers. In these, when not severe, we have daily a complete fit; but as the fits increase in severity the fever becomes continuous, and as it again declines it first becomes remittent, and ultimately intermittent.²

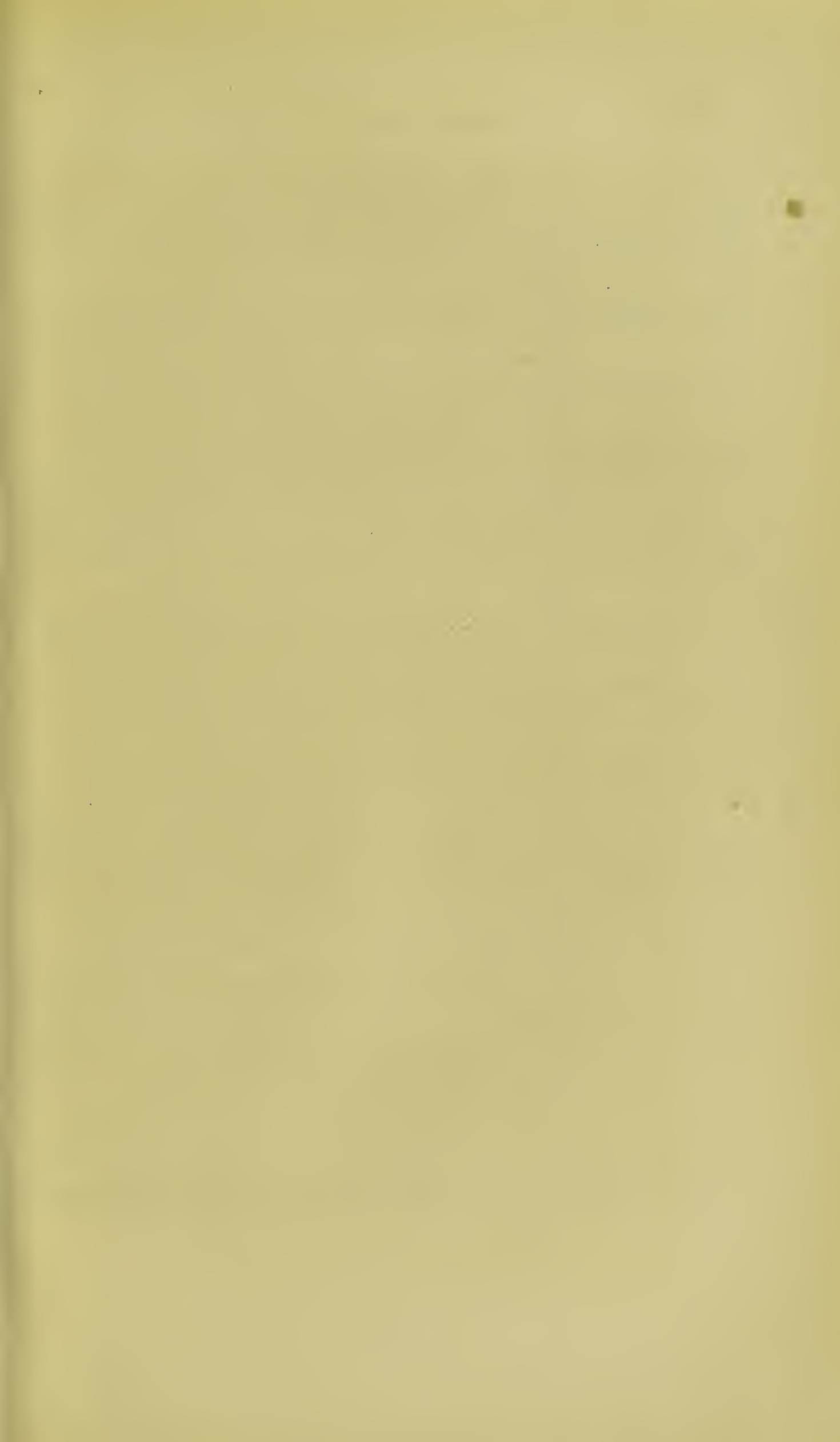
From the above it follows that, theoretically, we have no such thing as continued fever.

On looking over the above case, it will be seen that the time of the day at which the elevation of the temperature begins varies greatly; thus, it may begin early in the morning, and in rare cases its commencement may be postponed till 4 p.m. or even 9 p.m. If fevers be merely an exaggeration of the normal daily cycles, it follows the commencement of the fever will correspond to the commencement of the normal cycle of that day; this will account for the various hours of the day at which the fever first begins. In scarlet fever we can fix the commencement of the attack with the greatest precision, as is well known; it may begin at almost any hour of the day; thus, in the cases given, it began in one case at 1 a.m., two cases during the morning, one case at 11 a.m., three cases at 12 a.m., one case at 2 p.m., four cases at 5 p.m., one case at 10 p.m., one case during the night.

By observing the variation in the elevation of the temperature, we may learn the variations in health; from this we see that the period of the day at which the temperature reaches its maximum varies greatly on different days of the

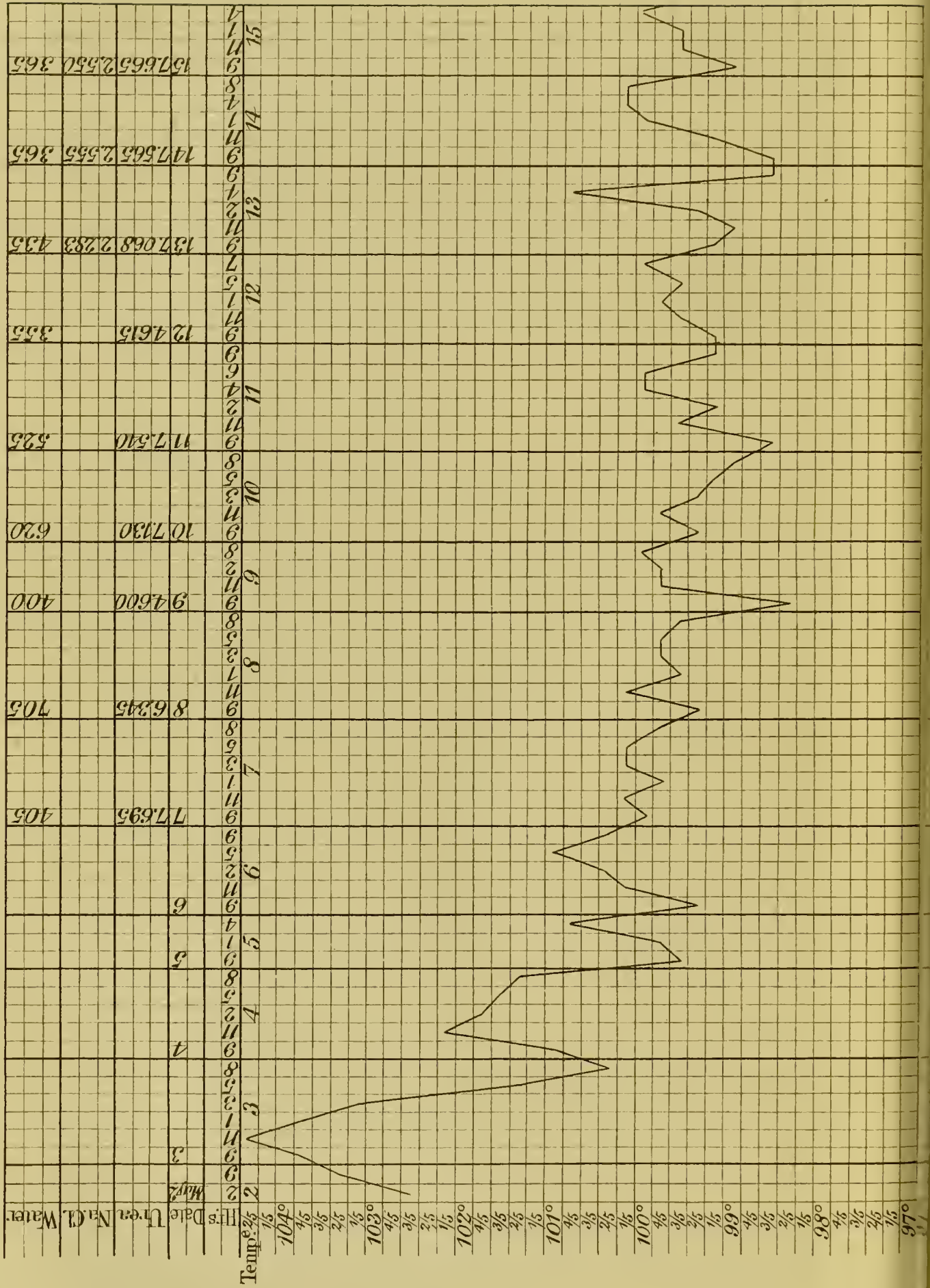
¹ Not only have we in these cases a distinct fit as regards the temperature, but also as regards the symptoms, there occurring in these cases a distinct hot and sweating stage daily.

² 'Wood,' vol. i, p. 240.



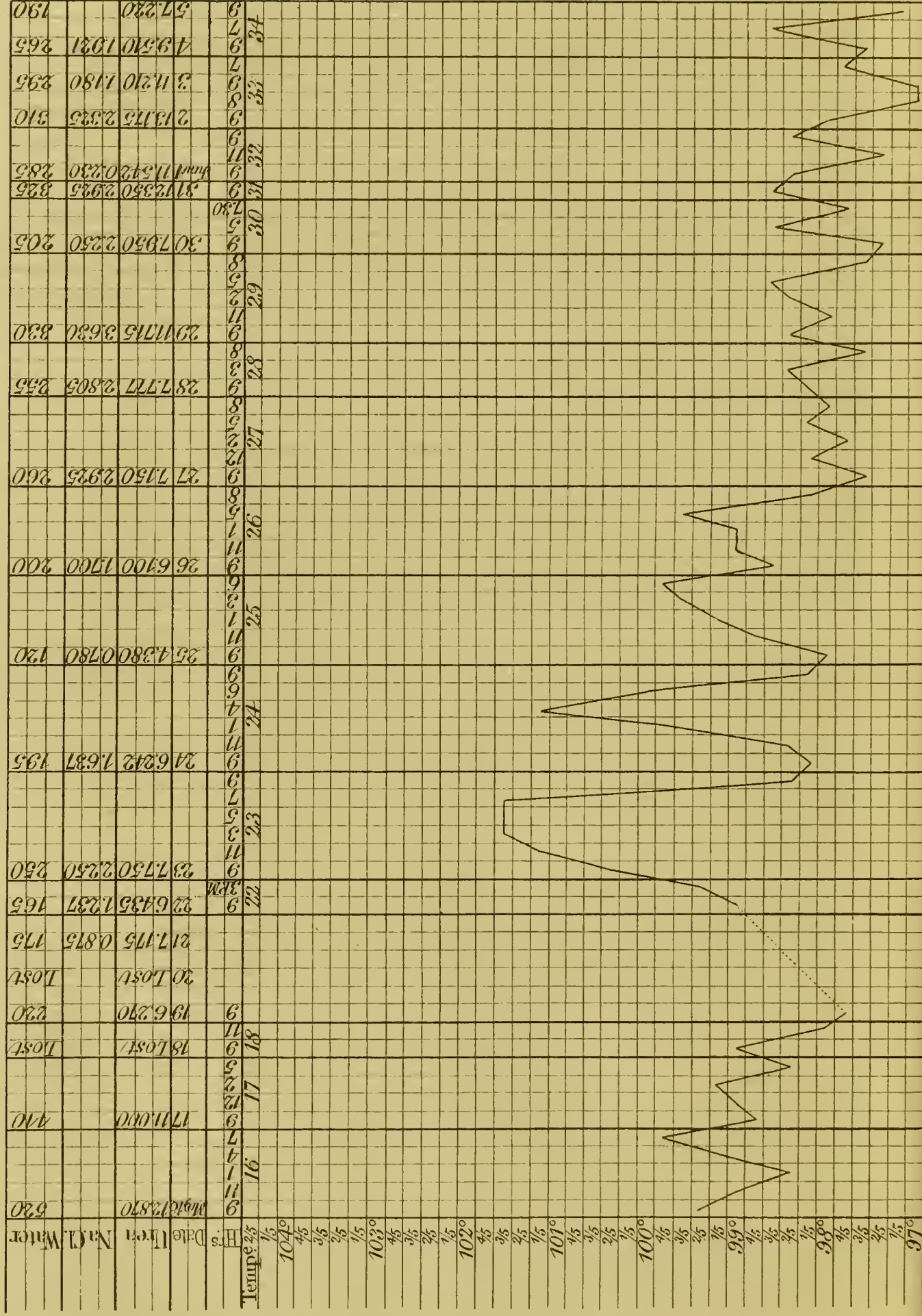
Case 1. Henry Maylin.

Nº 1A



Henry Maylin, *Cont'd.*

No. 1 B



Wtęstę

same case ; thus, it may reach its maximum at 9 a.m., or as late as 10 p.m., or at any other intermediate hour.

Dr. Edward Smith has shown that there is a daily capacity for increased tissue change. He has endeavoured to show that this occurs during midday ; from the above cases it appears that it may occur at any hour of the day.

The cases from which the preceding deductions are made are now added. I have been obliged to omit many of the charts of temperature, owing to the great expense. The Council of the Society, have, however, kindly allowed me to retain the most typical.

CASE 1 (see Diagrams 1, *a* and *b*).—Henry Maylin, æt. 6 ; weight, 16 kilogrammes. He was seized at 5 p.m., May 1st, with shivering, and complained of some sore throat ; during the night he was heavy and feverish.

The rash appeared on the second day of the disease, and disappeared on the eighth. The rash was strongly marked on the second day of the disease ; from that time it gradually faded.

Desquamation began on the sixth day of the disease, was completed generally between twenty-second and twenty-sixth days, though some still continued on the hands and feet on the twenty-ninth day. The desquamation was most marked under the clavicles and over the pubes.

The conjunctivæ were very much injected on the second day of the disease ; this then declined, and ceased on the seventh day.

The glands at the angle of the jaw were found to be rather enlarged on the second day. From the sixth to the eighth days inclusive they were still more enlarged, and, indeed, increased in size till the twenty-third day. On the twenty-sixth day they had begun to diminish. Glands down the upper half of the neck posterior to the sternomastoid were rather enlarged and shotty till the twenty-sixth day of the disease, when they were found to be normal. Glands in groins were found to be enlarged on the second day ; they increased in size till the seventh day inclusive,

after which they diminished, and became normal between the twenty-second and twenty-sixth day of the disease.

The tongue was thickly coated on the second day; from the fourth to the sixth inclusive it was of the well-marked strawberry kind; after this it improved, and became normal on the eleventh day.

The tonsils were vividly red and swollen till the fourth day; all redness had disappeared on the eleventh day, but they were found still enlarged on the twenty-fourth day.

The boy's appetite improved on the fourth day, and remained good till the twenty-second; on the twenty-eighth day it again became excellent.

Heart was healthy on the sixth day; no other note was made until the eleventh day, when systolic basic murmur was heard audibly at the second left cartilage; this continued audible till the fourteenth day, and disappeared suddenly on the fifteenth; from this time to the time of his dismissal from the hospital his heart sounds continued normal.

Some cough was noticed on the seventh day of the disease; on the twenty-second day it was very troublesome, and had all the character of hooping-cough, and continued so till the time of his discharge.

The boy was delirious only on the night of the second day of the disease.

Urine.—The urine was examined daily; no albumen was found till the twenty-fourth day, on which day there was a very distinct cloud on boiling and adding nitric acid; after this it decreased in quantity and disappeared on the twenty-seventh day; subsequent to this the urine always remained free from albumen; no blood nor casts were detected.

General appearance.—Till the tenth day the lips were dry, and the boy heavy; after this he steadily improved, though very slowly so, till the nineteenth day, when he flagged again, and on the twenty-second was puffy about the face, and the angles of his mouth and along the nose were ulcerated; after the twenty-third day he improved, though he still looked puffy till the twenty-sixth day. There was no distinct pitting on pressure any time.

Diet.—Second day, beef tea 1 pint, milk 1 pint, wine 4 oz.; seventh day, pudding diet, wine 3 oz.; eleventh, wine 2 oz.; thirteenth day, fish; twenty-first, second meal diet, 2 oz. of meal, 3 oz. of potatoes.!

CASE 2.—Henry Johnson; height, 3 feet $1\frac{1}{2}$ inch; weight, 10 kilogrammes. The child was seized during the night of the 23rd of May.

The rash appeared on the second day of the disease, disappeared on the seventh.

Desquamation, which was slight and very superficial, began on the tenth day, still continued on the feet on the twenty-ninth day. Glands at the angles of the jaw were rather enlarged, even on the twenty-ninth day. Glandula concatenatæ were not enlarged till the ninth day; on that and the following day both they and the glands at both angles were enlarged; on the twelfth day they were normal on the right side, but continued enlarged on the left till the twenty-third. Glands in groins were shotty till the tenth day.

Tongue was very red with prominent papillæ from the fourth to the sixth day inclusive; it then improved, and became normal between the fourteenth and nineteenth days.

Fauces, &c., were red and swollen on the fourth; after this the parts improved, and were normal on the tenth day. Appetite was pretty good on the fifth day; after this it continued excellent.

Heart was healthy throughout.

Lungs.—There was some sonorous rhonchus on the fourth, fifth, and sixth days.

Urine was examined daily; it never contained any albumen.

General appearance.—Throughout the time he was under observation he looked quite well.

Diet.—May 26th, milk 1 pint, beef tea 1 pint, bread and butter; 31st, pudding diet; June 4th, broth diet; 10th, second meal diet; 16th, pudding diet, milk half pint.

Table showing the daily amount of urea, chloride of sodium, and urinary water, excreted.

Day of disease.	Urea.	NaCl.	Water.
	Grammes.	Grammes.	
Fifth	5·642	1·313	185 c.c.
Sixth	6·120	2·486	255
Seventh	8·100	4·050	360
Eighth	8·100	4·225	360
Ninth	7·965	1·485	270
Tenth	10·660	3·382	410
Eleventh	9·190	2·480	310
Twelfth	6·045	1·782	310
Thirteenth	7·695	2·389	405
Fourteenth	6·840	1·680	380
Fifteenth	Lost	Lost	Lost
Sixteenth	8·625	1·983	345
Seventeenth	8·407	1·778	295
Eighteenth	6·697	1·081	235
Nineteenth	4·702	1·650	165
Twentieth	7·055	2·695	245
Twenty-first	7·875	2·250	250
Twenty-second ...	7·370	1·650	220
Twenty-third	8·360	1·650	220
Twenty-fourth ...	8·750	2·625	250
Twenty-fifth	10·867	3·450	345
Twenty-sixth	7·095	2·257	255
Twenty-seventh ...	10·075	3·332	310
Twenty-eighth ...	9·440	2·802	295
Twenty-ninth	7·685	2·030	290
Thirtieth	8·000	1·875	250

The temperature reached its lowest point on the fifth day of the disease.

CASE 3.—John Franklin, æt. 11 years 6 months; assumed weight, 30 kilogrammes. The boy has felt poorly during the last fortnight, complaining of headache and sickness, but continued at his work till January 17th, on which day he vomited once or twice, and on the same evening the rash appeared.

Rash was general, second, third, and fourth days. Disappeared on fifth.

Desquamation began on the hand and leg on the eighth day, was general by the sixteenth; patient discharged on the

twenty-ninth. Desquamation then completed, except on the limbs.

Tongue thickly coated with white fur on the second day, was strawberry from the fourth to sixth inclusive. After this it improved.

The tonsils, pharynx, &c., were very red on the second and third days. They improved from the sixth.

The appetite improved on and after the sixth day.

The boy improved in appearance greatly on the fifth day.

The urine never contained any albumen.

Table showing the daily amount of urea, chloride of sodium, and urinary water excreted.

Day of disease.	Urea.	NaCl.	Water.
	Grammes.	Grammes.	
Third	11·160	0·465	310 c.c.
Fourth	15·624	1·176	420
Fifth	16·175	1·290	430
Sixth	Lost	Lost	
Seventh	11·882	2·425	485
Eighth	13·563	3·255	775
Ninth	15·960	3·657	665
Tenth	6·676	1·862	245
Eleventh	15·750	7·000	700
Twelfth	13·982	6·098	595
Thirteenth	14·965	8·200	820
Fourteenth	16·877	5·887	785
Fifteenth	15·562	7·750	750
Sixteenth	19·080	4·402	795
Seventeenth	22·370	4·698	895
Eighteenth	22·372	6·969	1010
Nineteenth	23·205	6·915	
Twentieth	19·550	6·375	850
Twenty-first	21·750	4·575	750
Twenty-second ...	22·230	6·184	780
Twenty-third	24·000	6·400	800
Twenty-fourth ...	22·500	8·190	900
Twenty-fifth	22·312	6·512	875
Twenty-sixth	25·440		1060
Twenty-seventh ...	23·010	6·016	885
Twenty-eighth ...	19·500	4·950	825
Twenty-ninth ...	27·502	6·755	965

The temperature reached its lowest point on the sixth day of the disease.

CASE 4.—William Stephens, æt. 5 ; height, 3 ft. 1 inch ; weight, 14 kilogrammes. On April 25th he vomited, complained of sore throat, and had a slight cough. On April 26th he had a slight blush of redness all over him ; this increased in intensity till April 28th. Admitted on the sixth day of the disease ; all the rash had disappeared, leaving a yellowish mottling. No desquamation occurred till the twenty-fifth day, when there was slight superficial but decided desquamation on the thighs, legs, and dorsum of feet ; none on the soles of the feet, slight also on both shoulders. No further note was taken till the twenty-ninth day, when all desquamation had ceased.

Glands at the angles of the jaw were very much enlarged from the sixth to the nineteenth inclusive ; they then declined, but still were too hard on the twenty-ninth.

Neck, first noted on the seventeenth, and to the twenty-second inclusive they were enlarged, that is to say, those close to the head, those immediately above the clavicle, were normal.

Groin, from the sixth to ninth inclusive, they were enlarged, hard, and shotty ; they then declined, and on the twenty-fifth were normal in size, but too hard. On the twenty-ninth the left were normal, but the right were still too hard. On the seventh and eighth days were seen several red, hard elevations, about the size of peas, not unlike bug-bites, but without any central black spot or trace of bite ; these were surrounded by a little ring of redness. The alæ of his nose were excoriated, and discharged at the time of admission, and continued in much the same state till the twelfth day, when it was rather better, but still remained red and excoriated till the twenty-fifth day, when they were all but healed.

Tongue thickly coated ; tip and edge red, with prominent papillæ, sixth to eighth day inclusive ; fur cleared off from the anterior part, but did not leave it red, on the ninth ; from the eleventh day inclusive it was normal.

Tonsils.—Tonsils, uvula, &c., very deeply injected and swollen, whole posterior fauces covered with a thick, tena-

cious, opaque-looking membrane, from the sixth to eighth day inclusive. The redness then declined and the membrane thinned away, till, on the fourteenth, the membrane was replaced by a more purulent-looking matter. On the fifteenth the parts were decidedly better, and on the nineteenth they were normal.

The child's appetite was bad till the eighth day inclusive; it then improved, and after the ninth day continued excellent.

Heart healthy throughout.

Some sonorous rhonchus on the seventh, eighth, and ninth days; lungs otherwise healthy.

Throughout the time he was in hospital the child looked tolerably well; rather pale.

Urine at no time contained any albumen.

The child was admitted on the sixth day of the disease. On the sixth day the temperature rose to $102\frac{3}{5}$; on the seventh to $102\frac{3}{5}$; on the eighth to $100\frac{3}{5}$; on the ninth to 100; and on the tenth to 99. After this it daily rose to 99 till the nineteenth day.

Table giving the daily amount of urea, chloride of sodium, and urinary water excreted.

Day of disease.	Urea.	NaCl.	Water.
	Grammes.	Grammes.	
Seventh	7·477		245 c.c.
Eighth	10·080		320
Ninth	5·740		205
Tenth	6·240		240
Eleventh	5·290		230
Twelfth	6·977		325
Thirteenth	5·945		290
Fourteenth	4·857		355
Fifteenth	6·300		420
Sixteenth	8·600		400
Seventeenth	7·540		580
Eighteenth	8·225		470
Nineteenth	8·505	2·391	315
Twentieth	10·360	3·420	380
Twenty-first	10·450	3·420	380
Twenty-second ...	11·895		390
Twenty-third	11·025		315

Day of disease.	Urea.	NaCl.	Water.
	Grammes.	Grammes.	
Twenty-fourth ...	12·425		350 c.c.
Twenty-fifth	10·020		380
Twenty-sixth	Lost		
Twenty-seventh...	8·640	2·764	270
Twenty-eighth ...	10·370	3·400	340
Twenty-ninth ...	9·715	2·827	290
Thirtieth	7·525	1·128	215
Thirty-first.....	6·880	1·612	
Thirty-second ...	9·310	4·650	490

CASE 5 (see Diagram 4).—Charles Macdonald, æt. 5½. Seized on September 25th; rash first appeared on the 27th; sore throat on the 26th. Rash was universal, and most remarked over the legs on the fourth day, then declined, and only a slight punctiform redness on the legs on the eighth day of the disease. Desquamation began about the ears and trunk on the eighth day. Glands at the angles of the jaw and in the groins were enlarged. Numerous sudamina noticed on the fifth day.

Tongue devoid of fur, rather red; papillæ rather prominent on the fourth day; tongue pale on the fifth and eighth days, and was normal on the eleventh.

Fauces, &c., rather red, but not swollen, on the fourth day. The redness disappeared, but they were rather swollen and covered with muco-purulent matter on the fifth day; natural on the eighth; no note taken between fifth and eighth days.

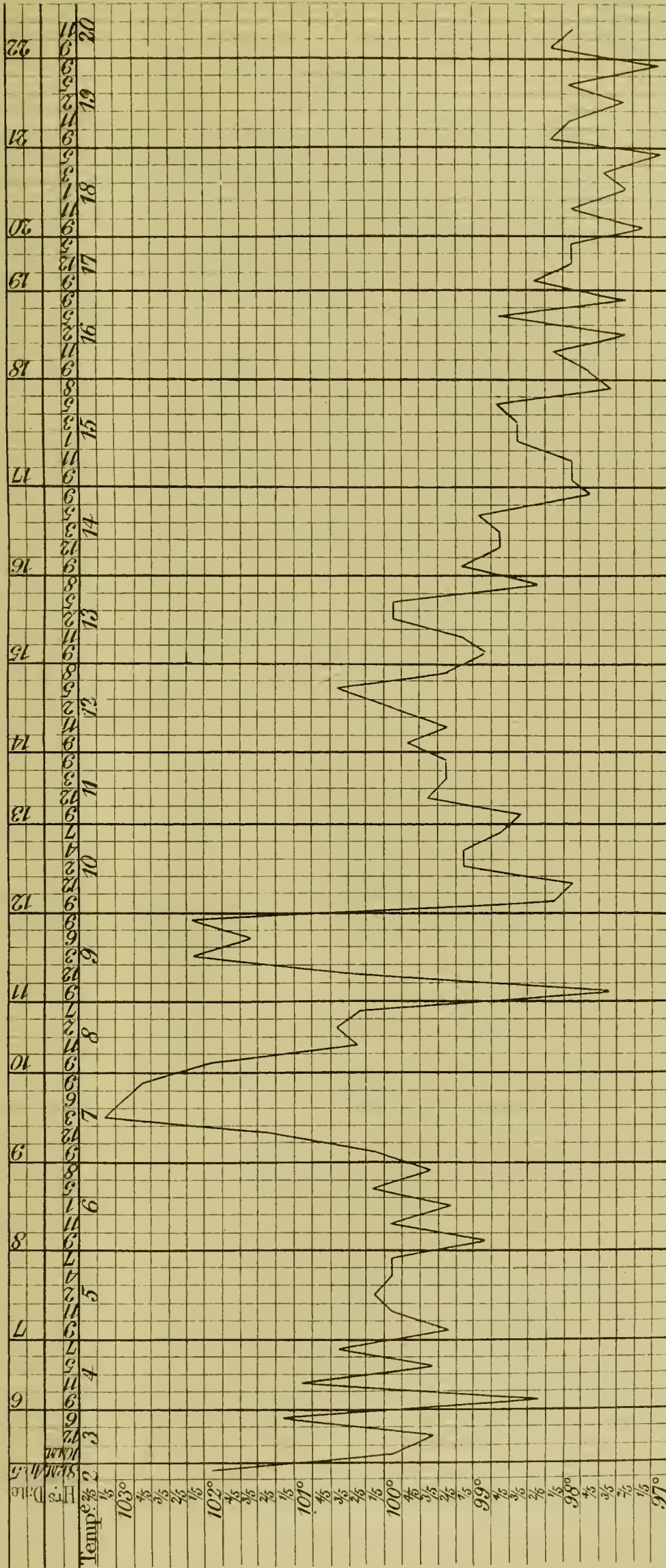
Appetite never bad.

Urine examined daily to the sixteenth day. No albumen at any time in the urine.

A very slight attack. Marked improvement was noticeable, however, with each fall of the temperature.

CASE 6 (see Diagram 3).—Thomas Stephens, æt. 4. Rash appeared on the second day of the disease, and lasted only one day. Desquamation began on the eleventh day. It had all but ended on the seventeenth day. On the third

Case 6: Thomas Stephens.



W. West 1884

day the child greatly improved, and continued to mend till the seventh day, when he became restless and dull. On the eighth day numerous wheals of urticaria appeared on his arms; these continued to appear till the eleventh day, on which day they had all disappeared.

Urine was tested daily. On the ninth day there was a slight cloud of albumen; tenth, ditto; twelfth, there was a very large quantity of albumen; thirteenth, enormous amount of albumen; fourteenth, ditto; fifteenth, the quantity of urine greatly increased, the albumen less; sixteenth, ditto; seventeenth, no albumen in the urine; eighteenth, distinct cloud discovered; nineteenth, slightest trace; twentieth and twenty-first, no albumen.

On the twelfth day the child was drowsy; on the fifteenth he was rather puffy about the face. At no time was there any pitting of the legs nor face on pressure.

Heart always healthy.

CASE 7.—Duchatel, male, æt. 5 years 6 months; was seized on October 12th, between dinner- and tea-time. Rash appeared on the thirteenth; on the third day of the disease the temperature reached 103° ; on the fourth, $102\frac{2}{5}$; on the fifth, $100\frac{4}{5}$; on the sixth, 101; on the seventh, 100; on the eighth, $98\frac{2}{5}$; on the ninth, 99; on the tenth, 98.

CASE 8.—Welsh, male, æt. 3 years 6 months. On the ninth day of the disease the highest temperature was $102\frac{1}{5}$; on the tenth, $101\frac{3}{5}$; on the eleventh, $103\frac{1}{5}$; on the twelfth, $102\frac{2}{5}$; on the thirteenth, $103\frac{1}{5}$; on the fourteenth, $101\frac{2}{5}$; on the fifteenth it fell throughout the day, and reached $99\frac{4}{5}$, and continued afterwards at about this temperature.

CASE 9.—Eliza Brown, æt. 11 years. Rash appeared on the second day. The urine contained no albumen during her stay in the hospital. On the second day of the disease the temperature rose to 102; on the third, 102; on the fourth, 99; and continued at this last temperature on all the following days.

CASE 10.—Anne Johnson, æt. 7; height, 3 ft. 5½ in.; weight, 16 kilogrammes. She first complained of some sore throat at dinner-time, May 25th, but continued in other respects in her usual health till tea-time, when she lay down and complained of headache and chilliness. During the night she was feverish and vomited.

The rash appeared on the second day of the disease, and disappeared on the sixth. Desquamation began on the sixth day of the disease, and was almost completed on the twenty-seventh. Some miliary vesicles were observed on the third day. The conjunctivæ were injected on the second and third days of the disease.

The glands at the angles of the jaw were never enlarged. The glandula concatenatæ were rather enlarged and hard till the twelfth day, when they were found to be normal. In the groins they were enlarged to the size of peas and beans; they became normal between the sixteenth and nineteenth days.

The tongue was very little affected; it was red, with prominent papillæ at the tip and edges, till the seventh day, and was normal on the twelfth.

The throat was vividly red and rather swollen on the second and third days. It became healthy on the eighth.

The appetite was bad till the seventh day, when it improved.

Heart was healthy till the fifth day, when a slight systolic basic murmur was heard. This disappeared between the twenty-second and twenty-seventh days.

The child was slightly delirious on the nights of the second and third days.

The urine was examined daily. It never contained any albumen.

General appearance.—The child never appeared at any time at all oppressed by the fever.

Diet.—May 26th, beef tea 1 pint, milk 1 pint, wine 4 oz. 28th, omit wine. 31st, pudding diet, milk 1 pint. June 4th, broth diet. 10th, meal diet.

The child was admitted on the second day of the disease.

On the second day of the disease the temperature rose to $102\frac{2}{5}$; on the third, 102; on the fourth, $100\frac{1}{5}$; on the fifth, $99\frac{2}{5}$; and continued to rise daily to this last temperature till the tenth, when it only reached 98.

Table giving the daily amount of urea, chloride of sodium, and urinary water.

Day of disease.	Urea.	NaCl.	Water.
	Grammes.	Grammes.	
Third	9·112	0·798	225 c.c.
Fourth	9·100	0·900	200
Fifth	6·075	0·911	135
Sixth	8·997	1·982	305
Seventh	6·090	1·450	290
Eighth	6·772	1·827	315
Ninth	Lost		
Tenth	7·680	2·400	480
Eleventh	7·695	2·025	450
Twelfth	7·905	2·325	405
Thirteenth	9·625	4·012	535
Fourteenth	10·875	4·350	580
Fifteenth	7·800	2·640	480
Sixteenth	8·407	2·675	415
Seventeenth	8·797	3·191	345
Eighteenth	8·400	3·990	420
Nineteenth	8·062	3·082	375
Twentieth	10·500	5·250	700
Twenty-first	11·812	3·370	375
Twenty-second ...	9·360	2·470	260
Twenty-third	11·000	3·212	440
Twenty-fourth ...	12·255	4·827	645
Twenty-fifth	11·115	3·700	390
Twenty-sixth	11·375	4·225	650
Twenty-seventh ...	12·670	4·870	650
Twenty-eight	12·420	3·510	540

CASE 11.—George Gibbs. No note was made of the date of the commencement, but merely of the day on which the rash appeared; this I have assumed to be the second day.

The rash disappeared on the eighth day; desquamation began on the eighth day, and was mostly completed on the twenty-seventh day. Some still remained on the feet and ankles till the thirty-ninth, and on the soles of the feet till the forty-seventh day.

Glands.—At the angles of the jaw they were enlarged; began to diminish on the eighth day, but were still somewhat enlarged on the thirty-first.

Groins, here they were so much enlarged as to be visible; they began to diminish on the ninth day, but were still spotty on the thirty-first.

Urine.—No albumen before and on the eleventh day; slight cloud on the twelfth; increased in quantity on the thirteenth; slight cloud from the fourteenth to the sixteenth inclusive; none on the seventeenth; none till the twentieth, on which day a large quantity was discovered. Still more albumen, urine smoky, on the twenty-first; albumen less, rather smoky, on the twenty-third; much more smoky on the twenty-sixth; very smoky, less albumen, on the twenty-seventh and twenty-eighth; less smoky on the twenty-ninth and thirty-first; not smoky, a slight cloud of albumen, on the thirty-fourth; very slight on the thirty-fifth; smoky, rather dense cloud of albumen, on the thirty-sixth and thirty-seventh; albumen less on the thirty-eighth; not smoky, and only slight cloud of albumen on the thirty-ninth and fortieth, and continued so to the forty-sixth day.

General condition.—Progressed favorably till the night of the eleventh, when he complained greatly of pain in the left ear, which continued during the twelfth day. Was puffy about the face, and pitted over the forehead on the twenty-second. This increased somewhat till the thirty-first day inclusive, and then declined.

Temperature.—On the second day of the disease the temperature reached to $102\frac{4}{5}$; on the third, $103\frac{3}{5}$; on the fourth, $101\frac{2}{5}$; on the fifth, $99\frac{2}{5}$.

It continued to rise daily to this point till the eleventh day, when it rose to 101. From the twelfth to the seventeenth days inclusive it never rose higher than $99\frac{2}{5}$.

The temperature was not taken on the eighteenth and nineteenth, but on the twentieth day it reached to $105\frac{1}{5}$; on the twenty-first, $99\frac{3}{5}$; on the twenty-second, $101\frac{1}{5}$; on the twenty-third, $99\frac{3}{5}$.

It then continued at about 99 till the twenty-sixth day

when it again rose to $103\frac{2}{5}$. From the twenty-seventh to the fortieth day it remained at about 99.

CASE 12.—Ann Swinson ; height, 3 feet 6 inches ; weight, 16·3 kilogrammes. She was admitted for supposed caries of the crest of the ilium. The scarlet fever developed itself whilst she was in the hospital.

On March 25th she had sore throat, and flagged. On the 27th, a doubtful rash was seen. She had no desquamation, and the reality of the nature of the disease was considered doubtful till the renal affection presented itself.

On the nineteenth day of the disease, between 6 and 7 a.m., seized with vomiting and shiverings ; the evening before she was pretty well. At the time of my visit she was oppressed, drowsy, very pale, and puffy. She complained of much frontal pain, and had lost her appetite. Pulse 176, respiration 48. Wounds about the ilium looking as before. Lungs were healthy. During the morning she perspired very profusely, and at 12 a.m. her trunk was covered with minute sudamina.

On the twentieth day was much improved ; complained of no pain anywhere. Rather drowsy ; appetite very bad ; pulse 116, very weak ; wounds looking much the same. Last night, about 7 p.m., complained of much pain in right foot ; there was no redness nor swelling, but it was very tender. This morning there is a deep-red blush over the malleoli, and this part is very tender. Appetite very bad.

On the twenty-first she was less puffy, complained of no pain ; pulse 132, feeble. Redness over the right ankle increased in intensity and area ; the wounds about the crest of the ilium were looking well ; appetite was better than yesterday ; less drowsy.

Twenty-second.—Passed a restless night ; still rather puffy ; ankle more swollen, very red, and painful ; pulse 108, weak ; lungs healthy ; heart, first sound at the apex murmurish.

Twenty-third.—Matter pointing over the outer malleolus ; appetite a little better ; still puffy looking.

Twenty-fourth.—Much the same ; first sound of the heart at the apex dull.

Twenty-fifth.—Swelling extending up the leg.

Twenty-sixth, 3 a.m.—Active vomiting came on, greenish colour, accompanied with diarrhœa ; lips and tongue rather dry ; soft systolic apex murmur ; ankle opened.

Twenty-eighth.—Much thin discharge from the wound at the ankle ; redness very much less ; no sickness, no diarrhœa.

Thirty-first.—Face pasty looking ; tongue dry ; discharge from ankle less. No pitting of any part of body, except right foot ; distinct apex systolic murmur.

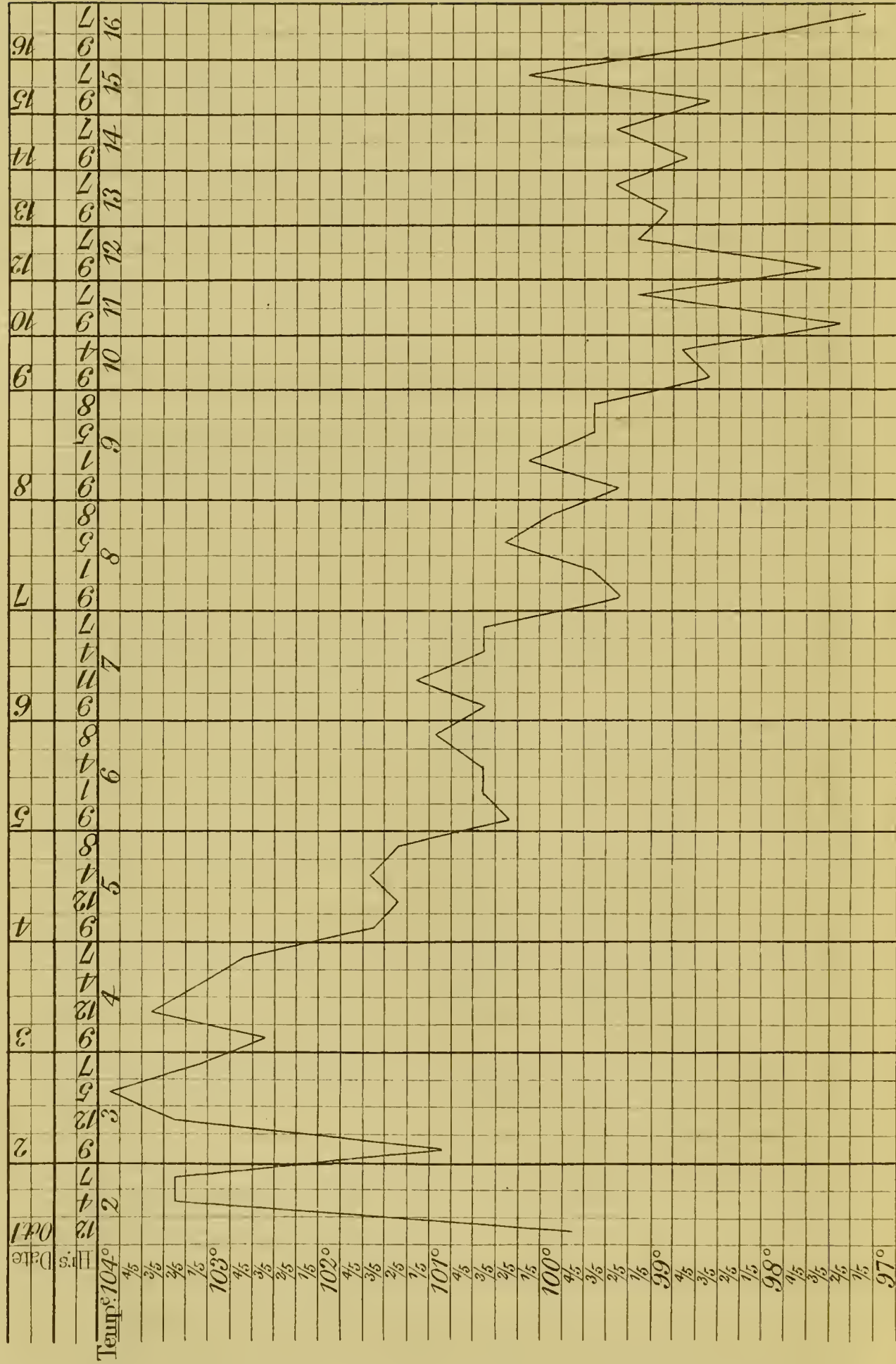
Thirty-second.—Decidedly better.

Subsequently active tubercular deposition took place in her lungs.

Urine.	Urea.	Quantity.	Albumen.
5.30, March 27th, to 10 a.m., March 28th	4.779	117	
Fifth day, March 28th and 29th ...	4.720		Shade.
Sixth	3.877	235	Slight shade.
Seventh	5.037	310	Slight shade.
Eighth	6.020	430	Slight shade.
Ninth	7.59	660	Rather more.
Tenth	7.450	745	Shade.
Eleventh	11.325	1175	Shade.
Twelfth	11.325	1175	Shade.
Thirteenth	8.712	1025	Shade.
Fourteenth	9.776	1185	Shade.
Fifteenth	9.150	915	Shade.
Sixteenth	8.085	735	None.
Eighteenth	10.442	585	None.
Nineteenth	7.995	390	None.
Twentieth.—Smoky, red colour			Abundant.
Twenty-first.—Slightly smoky			Very abundant.
Twenty-second	1.875	110	Fills two thirds of the tube.
Twenty-third	0.510	60	Fills two thirds of the tube.
Twenty-fourth.—Albumen much less		85	
Twenty-fifth.—Urine contains casts and uric acid, and also kidney-epithelium.			
Twenty-sixth.—Albumen much more abundant.			
Twenty-seventh. — Albumen much more abundant.			

Case 16. Ellen Kepping.

No. 4.



W. West bidel

On the twenty-second and twenty-third days the albumen was removed by shaking up the urine with animal charcoal.

She was readmitted on the seventy-eighth day; the urine still contained abumen.

Temperature.—On the third day the temperature reached $100\frac{3}{5}$; on the fourth, $98\frac{3}{5}$; on the fifth, $98\frac{3}{5}$; on the sixth, $98\frac{1}{5}$; on the seventh, $100\frac{1}{5}$; on the eighth, $100\frac{1}{5}$; on the ninth, $100\frac{3}{5}$; on the sixteenth, 99; on the seventeenth, 97; on the eighteenth, $98\frac{3}{5}$; on the nineteenth, 105; on the twentieth, 100; on the twenty-first, $101\frac{3}{5}$; on the twenty-second, $103\frac{1}{5}$; on the twenty-third, $101\frac{4}{5}$; on the twenty-fourth, 102; on the twenty-fifth, $100\frac{4}{5}$; on the twenty-sixth, $100\frac{4}{5}$; on the twenty-seventh, $101\frac{4}{5}$; on the twenty-eighth, $102\frac{1}{5}$.

CASE 13.—Charles Ebett, æt. 3 years 9 months. The commencement of the disease in this case was not noted, but merely the first appearance of rash. This I have assumed to be the second day.

This was a very slight case.

Temperature.—On the second day of the disease the temperature rose to $101\frac{2}{5}$; on the third, $99\frac{4}{5}$; on the fourth, $99\frac{3}{5}$; on the fifth, $97\frac{4}{5}$; on the sixth, $97\frac{2}{5}$.

CASE 14.—Matilda Browne. The lowest temperature occurred on the fifth day, the temperature falling from $102\frac{2}{5}$ to 100.

CASE 15.—Sarah Hewett, æt. 7. She was seized on 7th, shortly after breakfast. The rash appeared on the second day.

The temperature on the third day rose to 101; on the fourth, to 100; on the fifth, to 99.

CASE 16 (see Diagram 4).—Ellen Kipping, æt. 11. Seized Monday, September 30th, with vomiting, diarrhœa, anorexia, and complained of sore throat. Rash first noticed on October 1st. It was intensely marked. It had nearly

disappeared from the whole body on the seventh. Desquamation began on the ninth, about the forehead and labia. Tongue was rather furred on the second day, thickly coated on the third; after this it was of the strawberry character to the ninth inclusive; after this no notes were made.

Fauces were vividly red, but not swollen, to the fifth day inclusive, and improved on the eighth.

Conjunctivæ were injected till the seventh day inclusive.

Glands at the angles of the jaw were slightly enlarged; more so in groins.

Urine was tested till the ninth day; on the fifth and sixth there was a slight trace of albumen.

The child was rather delirious during the fourth and fifth nights.

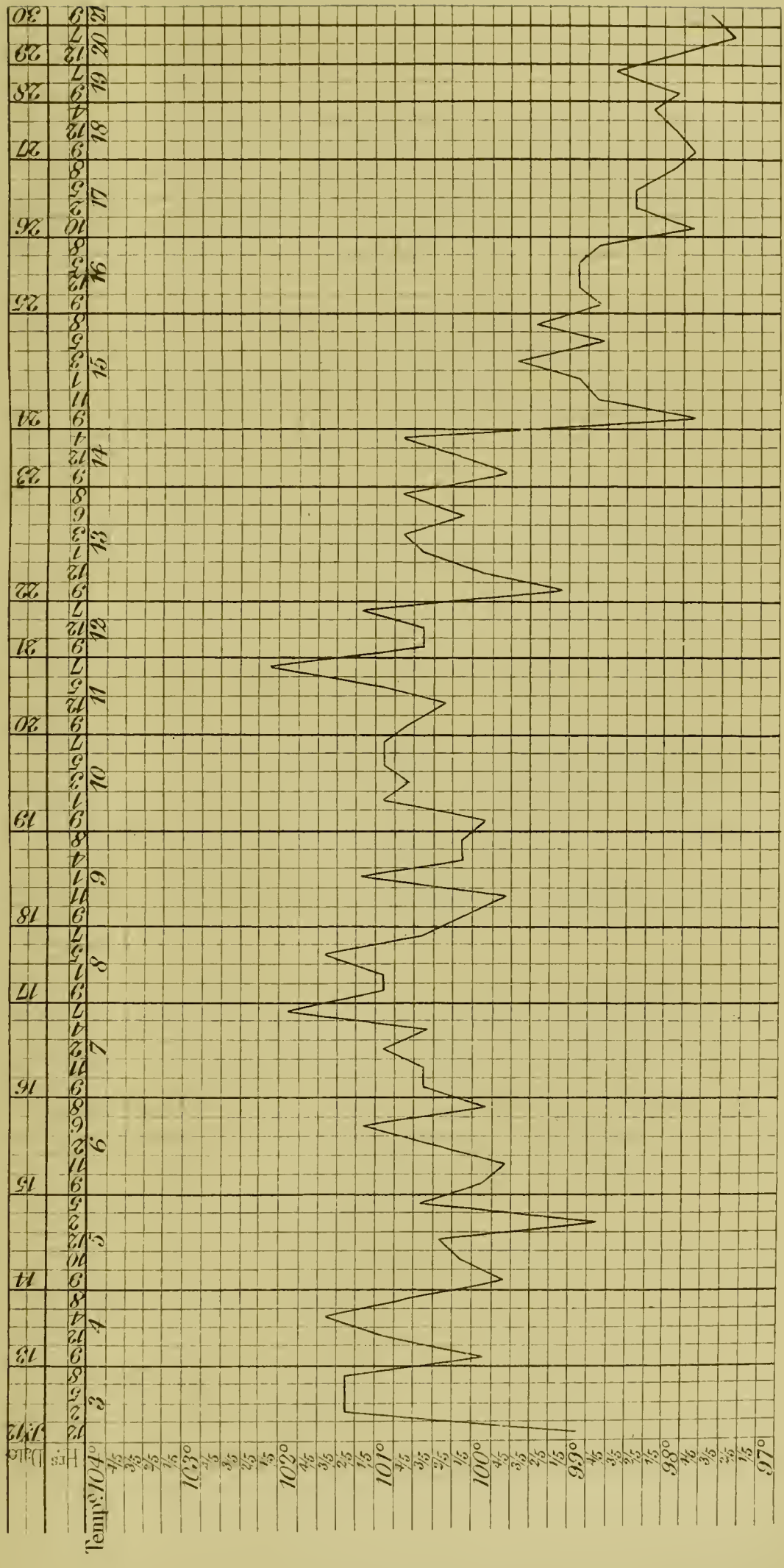
Appetite was very bad till the sixteenth, when it improved somewhat.

This was decidedly a sharp attack. The rash was strongly marked. She was very heavy and prostrate till the fifth day, when she very greatly improved, and then continued to mend.

CASE 17 (see Diagram 5).—Maria Hodge, æt. 2 years 2 months. Scarlet fever, urticaria, chicken-pox. The child had an attack of measles three weeks before her admission into hospital. The attack lasted about a week, and then she appeared quite well again. On July 19th was quite well during the day, but was very restless during the night. Next day the rash appeared, and she was feverish and had no appetite. Rash at the time of admission was slight everywhere, but most marked on the legs. It disappeared from the face, chest, and abdomen on the fifth day, and from the legs and arms on the seventh. In this case the rash on the arms and legs was much localized, and caused hard, spotty elevations, some the size of a small pea; it was in these that the rash remained so long.

Desquamation.—Face, none; trunk, none. Legs, appeared on the folds of thighs on the eighth, and disappeared on the ninth. Appeared on the arms slightly on the ninth, dis-

Case 17. Maria Hodge.



W. West bbb.

appeared on the tenth; on the sixteenth there was some on the palms of the hands.

On the seventh day of the disease a wheal of urticaria was noticed; a few more appeared on the eighth and ninth. They consisted of elevations about the size of peas, pale, semi-transparent, hard, and surrounded by a ring of redness an inch in diameter.

On the seventh a vesicle of chicken-pox was seen on the chest, followed by a few others till the twelfth day inclusive. These, instead of drying up and healing, ulcerated and became surrounded by much swelling. The ulcers began to heal on the fifteenth day.

Alæ of nose became excoriated with a thin, sanious discharge on the seventh, continuing much the same till the thirteenth, when it improved gradually to the eighteenth day.

Tongue thickly coated, red on the third day, then cleaned; papillæ were prominent on the anterior part still on the fifteenth; was normal on the ninth.

Fauces, &c., very red and swollen, fourth and fifth days; still more so, and covered with muco-purulent-looking matter, on the sixth to eighth inclusive. They then improved, and were almost normal on the eighteenth.

Appetite improved on the fourth day, and continued good after the fifth.

Glands at the angles of the jaw were not enlarged; on the third day began to enlarge; on the fourth they increased in size, till the enlargement was visible on the eighth; they then decreased, and were almost of natural size on the eighteenth. In groin they were first enlarged on the fifth day, and continued slightly enlarged till the ninth, after which they were of normal size.

Urine was examined daily till the twenty-ninth day; no albumen was at any time discovered.

The child appeared to be in a very delicate state and the lips were very dry on the third, cracked and swollen on the eighth and ninth; they then improved somewhat.

On the fifth day a decided improvement, however, was noticed; on the sixth, seventh, and eighth, was not so well

again; vomited. She continued very poorly and heavy during the eleventh and twelfth. After this the child improved.

CASE 18.—Eliza Cunningham, æt. 7; assumed weight, 16 kilogrammes. The patient was in the hospital for epilepsy at the time of her seizure. On April 24th, at 11 a.m., she complained of headache and sore throat; soon after, she vomited. After this she appeared to be in her usual health till 4 p.m., when she again vomited, and on being undressed to be put to bed the rash was detected.

Thus the rash appeared on the first day, and disappeared on the eighth day.

Desquamation began on the ninth day and had ceased everywhere on the twenty-eighth day, except on the hands and feet.

Eyes were much injected with some muco-purulent-looking discharge from the second to the sixth day inclusive; it then declined, and ceased on the eleventh day.

Glands.—Angles of jaw were enlarged from the second to eleventh days inclusive, then the swelling declined, and disappeared between the twenty-fourth and twenty-eighth.

The glands of the neck were also enlarged, hard, and spotty.

Groins.—A little hard on the second day, enlarged on the third; still more, so as to be visible, during the fourth and fifth; then the swelling declined, and ceased between the twenty-fourth and twenty-eighth days.

Numerous ecchymoses noticed under the clavicles and in groins on the fourth and fifth days.

Some miliary vesicles appeared on the fourth and fifth days.

Sudamina appeared on the eighth day, and were still more numerous on the ninth.

The child was delirious during the night of the first to the fourth inclusive.

Tongue was thickly coated with a creamy fur, the papillæ being prominent on the second and third day. Well-marked

strawberry on the fourth and fifth; it then improved, and was natural on the seventeenth.

Fauces, &c., were very red; on the second day after this the parts improved, and were almost normal on the sixth, continuing, however, a little red and flabby till the tenth.

Heart and lungs healthy throughout.

Pulse was found to be irregular on the twenty-fourth to twenty-eighth days; no other notes made.

General appearance.—Child was heavy and dull on the second day; lips were dry and excoriated on the third; looked better on the fourth day; was decidedly so on the fifth; sat up in bed and played. Then improved till the ninth, when she looked puffy and was rather drowsy. This continued till the twelfth inclusive. After this she improved, though she long continued to be very pale.

There was no albumen in her urine at any time.

Diet.—April 27th, beef tea 1 pint, milk 1 pint, wine 4 oz. May 4th, pudding diet, wine 3 oz. 11th, fish, wine 2 oz.

Temperature.—On the second day of the disease it reached 105; on the third, $105\frac{1}{5}$; fourth, $104\frac{1}{5}$; fifth, $102\frac{2}{5}$; sixth, $102\frac{2}{5}$; seventh, $103\frac{1}{5}$; eighth, $101\frac{1}{5}$; ninth, 101; tenth, 101; eleventh, $100\frac{2}{5}$; twelfth, $99\frac{2}{5}$; thirteenth, $99\frac{1}{5}$; fourteenth, $99\frac{2}{5}$; fifteenth, $98\frac{3}{5}$. It continued at about $98\frac{3}{5}$ till the twenty-third day, after which it was not taken.

Table showing the daily amount of urea and urinary water.

Day of disease.	Urea.	Urinary water.
	Grammes.	
Third	13·950	450 c.c.
Fourth	14·550	485
Fifth	15·240	635
Sixth	8·972	485
Seventh	8·910	810
Eighth	10·290	980
Ninth	5·898	715
Tenth	5·665	515
Eleventh	5·197	385
Twelfth	6·050	550
Thirteenth	4·567	435

Day of disease.	Urea.	Urinary water.
	Grammes.	
Fourteenth	6·825	350 c.c.
Fifteenth	7·312	325
Sixteenth	6·195	590
Seventeenth	8·550	450
Eighteenth	Lost	
Nineteenth	10·135	280
Twentieth	10·360	280
Twenty-first	9·350	275
Twenty-second ...	10·767	365
Twenty-third	9·657	365
Twenty-fourth ...	10·725	330
Twenty-fifth	11·700	325
Twenty-sixth	12·240	360
Twenty-seventh...	9·460	220
Twenty-eighth ...	9·800	245
Twenty-ninth	11·812	315
Thirtieth	6·982	245
Thirty-first	7·020	390
Thirty-second ...	12·410	730

CASE 19 (see Diagram 6, *a* and *b*).—Anne Lynch, æt. 3 years 3 months. On April 28th she had rigors. Lost her appetite, and subsequently was very thirsty.

On April 29th the rash appeared. She never complained of sore throat. The rash disappeared on the tenth day.

Desquamation began on the seventh day; it had mostly ceased on the twenty-fourth, but still continued on the heel on the forty-third day of the disease. It also continued on the palms of the hands till the thirty-sixth day.

Numerous miliaria were observed over the whole body, except the hands, arms, and feet, on the fourth and fifth days.

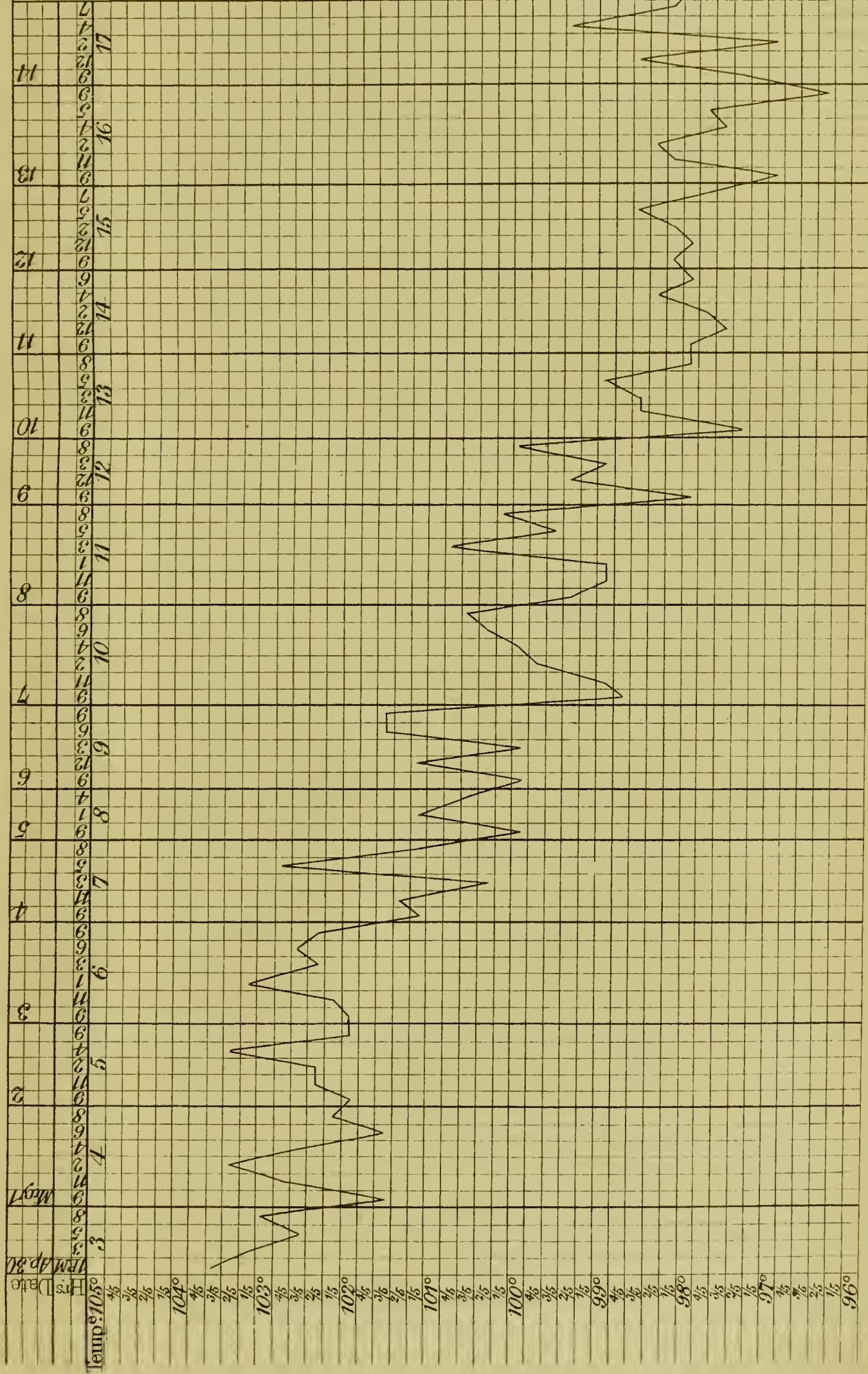
Glands at the angles of jaw were rather enlarged on the third and fourth days, and greatly so from the fifth to the eighteenth days inclusive, those on the right side being the most so. They decreased in size from the twenty-second, though on that day they were as large as a chestnut. They were still enlarged on the fifty-first day.

The glandula concatenatæ on both sides were enlarged.

In the groin they were rather enlarged from the third to

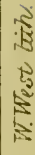
Case 19. Anne Leach.

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the twenty-ninth day ; after this they decreased, and were normal on the thirty-sixth.

Tongue was red, with prominent papillæ on the fourth. It then improved, and on the eighth and ninth it was pale and smooth. After the sixteenth day it was normal.

Fauces, &c., lividly red ; tonsils much enlarged, and covered with exudation ; much muco-purulent-looking fluid over the posterior fauces from the third to the ninth day inclusive. They were less red, and some exudation was observed on the posterior surface of the uvula on the eleventh day. The tonsils were so swollen as almost to meet on the thirteenth and fourteenth days. A small ulcer was noticed on the palate from the sixteenth to the eighteenth days inclusive. The swelling diminished in size from the twenty-second, and were almost natural on the twenty-fourth.

Appetite was bad till the fourteenth day inclusive. It was excellent from the eighteenth to the twenty-ninth inclusive. On the thirty-third it was bad again, and continued so on the thirty-fourth and thirty-fifth, after which it improved again.

A discharge from the right ear began on the thirty-sixth, and continued till the forty-third day.

Heart was healthy throughout.

Some sonorous rhonchus heard in the lungs on the fifth day.

There was no pitting of the forehead, sacrum, nor legs, on pressure, at any time.

General appearance.—The child was oppressed till the eighth day. After this she improved, and continued pretty well till the thirty-fourth day, when she became very ill again. She was very drowsy from the thirty-third to the thirty-sixth day inclusive.

Urine was examined daily on the twenty-third for the first time ; a distinct cloud of albumen was noticed.

Twenty-fourth.—More abundant.

Twenty-sixth.—Still more abundant.

Twenty-seventh.—After boiling and being allowed to stand, the coagulated albumen filled one third of the tube.

To-day, for the first time examined microscopically, a little blood was found, and some uric-acid crystals.

Twenty-eighth.—Albumen fills one half of the tube.

Twenty-ninth.—Albumen same in amount; urine contained blood; casts waxy and granular.

Thirtieth.—Urine very smoky; albumen about the same; contained blood and casts.

Thirty-first.—Of a red colour, evidently due to blood; albumen the same; contained casts, blood, and uric-acid-crystals.

Thirty-second.—Less smoky; albumen a little less; blood, uric acid, casts.

Thirty-third.—Albumen fills one fourth of the tube. Blood appears to be much more abundant; casts and uric acid.

Thirty-fourth.—Albumen same, judging by the colour and the amount of deposit; the blood much more abundant.

Thirty-fifth.—Same.

Thirty-sixth.—Albumen fell one third of tube; urine still redder; casts, with blood, pus, and kidneys; epithelium imbedded in them, also some free from corpuscles.

Thirty-seventh.—Urine very much better, much less red; deposit of blood much less abundant; albumen occupies about one seventh of the tube; cast and pus-cells.

Thirty-eighth and thirty-ninth.—Ditto.

Forty-first.—Albumen less now, merely smoky, and rather red; albumen fell one twelfth of tube.

Forty-second.—Urine better.

Forty-fourth.—An abundant cloud of albumen; urine still pinkish and smoky.

Forty-sixth.—Not smoky. Rather abundant cloud of albumen.

Forty-seventh.—Much more smoky again.

Forty-eighth.—Blood appears to be much more abundant again. Rather thick cloud of albumen. Microscope—blood-casts and plenty of kidney-epithelium.

Forty-ninth.—Still worse, redder, and brown. Very abundant precipitate of blood. Abundance of urine passed.

Fifty-first.—Still very smoky and red.

Fifty-second.—Still very red, and copious deposit of blood. On boiling did not get a trace of albumen.

Fifty-third.—Ditto.

Fifty-fourth.—Ditto but got a decided cloud of albumen, when urine shaken so as to mix the blood with it.

Fifty-fifth.—Same.

Fifty-sixth.—Decidedly better, scarcely smoky. No deposit of blood.

Fifty-seventh.—Urine still less smoky; amount of albumen greatly increased.

Fifty-eighth.—Not smoky; an abundant cloud of albumen.

Sixty-first.—Not smoky; albumen rather less.

Sixty-third.—Urine abundant; distinct cloud of albumen.

Sixty-fifth.—Again red and smoky, with rather abundant cloud of albumen.

Urine always abundant.

CASE 20.—Louisa White; height, 3 feet 5 $\frac{1}{4}$ inches; weight, 15·4 kilogrammes. She was in the hospital with a slight attack of chorea, and was discharged on account of the prevalence of diphtheria, but was very soon readmitted with scarlet fever.

She was seized with sore throat on March 12th. The rash appeared on the same day, and on the first day the rash was over the whole body except the feet.

Second day it reached the feet, elsewhere declining. Disappeared from the face on the third day; from the forearm on the fourth; from the legs on the fifth; from the shoulders and all the body, except immediately beneath the clavicles and over the pubes, on the sixth, and on the seventh it had universally disappeared.

Desquamation began on the seventh day on the face and neck; on the eighth day it implicated the entire trunk and arms; on the ninth it began on the palms of the hand; on the fourteenth on the thighs; sixteenth, on the fore legs, and at the same time it was completed everywhere else except on the hands.

Twenty-ninth.—Almost completed on the palms.

Thirty-sixth.—Still desquamating on the soles of the feet.

The conjunctivæ were injected on the first, second, and third days.

Glands (angle of jaw.)—They were rather enlarged on the first day; they increased in size till the tenth day; between this and the twenty-sixth they became normal.

Glands in the groins were much enlarged, so as to be visible, and on thirty-first day were still enlarged.

Glands of neck were also enlarged.

Tongue red, with patches of fur, on the first day. From the second to eighth inclusive it was strawberry; on ninth and tenth day pale, and rather dry. Became moist on sixteenth, and then was a little red, and continued so to thirty-sixth, when it was still smooth in the centre.

Fauces red and inflamed on the first day; increased in size, so that the tonsils almost met, till the third. On the fourth the parts were covered with a tenacious-looking membrane. On seventh, besides the above membrane, there was much muco-purulent-looking fluid. On tenth, tonsils were less swollen; after this declined till on the fifteenth its parts were only slightly swollen and red.

No delirium on the first night. Delirious during the second, third, and fourth nights.

Appetite very bad till the ninth day, when it improved and continued good afterwards.

Lips, nose, &c.—First day sordes on lips; this continued, and on the fifth, lips were drier and the alæ of the nose became red and excoriated. After the eighth day these improved somewhat, but nose continued red and excoriated and the lips dry till the twenty-fifth day.

Choreac movements became worse somewhat on the third, fourth, and fifth days. Much better on sixth, and ceased on the seventh; continued so till the twenty-seventh, when they were slight, and then disappeared again, not returning up to the time of her dismissal. Her movements, however, throughout were awkward.

Child was very ill and did not improve till the tenth day, when a slight improvement was noted, and convalescence after this was very slow till the twenty-eighth day, when a decided improvement was noticed.

No albumen in the urine at any time.

Temperature.—On the tenth day the temperature rose to $103\frac{3}{5}$; on the second, to $103\frac{2}{5}$; on the third, to $102\frac{3}{5}$; on the fourth, to $100\frac{2}{5}$; on the fifth, to $100\frac{3}{5}$; on the sixth, to $101\frac{3}{5}$; on the seventh, to $100\frac{3}{5}$; on the eighth, to $101\frac{3}{5}$; on the ninth, to $102\frac{3}{5}$; on the tenth, to $102\frac{3}{5}$; on the eleventh, to $102\frac{1}{5}$; on the twelfth, to $101\frac{3}{5}$; on the thirteenth, to $99\frac{3}{5}$; on the fourteenth the temperature continued about 99 till the fortieth day.

Table showing the daily amount of urea, chloride of sodium, and urinary water.

Day of disease.	Urea.	NaCl.	Water.
Second	7·370	0·440	220 c.c.
Third	10·650	0·600	300
Fourth	10·608	1·035	345
Fifth	9·800	0·980	280
Sixth	9·300	1·035	345
Seventh	9·300	1·705	620
Eighth	9·347	1·110	370
Ninth	8·200	1·840	400
Tenth	5·880	1·120	280
Eleventh	7·425	1·320	330
Twelfth		Lost.	
Thirteenth	7·245		345
Fourteenth	7·065	2·363	305
Fifteenth	4·140	1·350	180
Sixteenth		Lost.	
Seventeenth	7·567		322
Eighteenth	5·200		200
Nineteenth	7·227		245
Twentieth	5·565		210
Twenty-first	7·055		415
Twenty-second ...	7·930		305
Twenty-third	7·287		275
Twenty-fourth ...		Lost.	
Twenty-fifth ... } Twenty-sixth.. }	11·100		555
Twenty-seventh ...	5·865		345
Twenty-eighth ...	6·410		435
Twenty-ninth	7·827		505
Thirtieth	9·067		585
Thirty-first	10·005		435
Thirty-second ...	8·580		520
Thirty-third	8·100		360
Thirty-fourth	6·743		415
Thirty-fifth	12·610		485
Thirty-sixth	11·760		480
Thirty-seventh ...	8·500		500

CASE 21.—Anne Neil. Rash appeared on the 27th April. No rash at any time on the face.

Chest.—Numerous reddened, elevated papillæ, from the second to the fifth day inclusive. After this it declined, and had disappeared on the ninth.

Abdomen.—Same as on chest, except that it commenced to decline on the fifth, and some slight rash still continued on the ninth day.

Legs the same as the abdomen.

Desquamation.—No note was made on the ninth and tenth days, but on the eleventh it was slight on the chin and chest.

Glands at both angles of the jaw were enlarged slightly on the second day; those on the left side continued slightly enlarged till the thirteenth, when they were normal; those on the right side, after the second day, increased greatly in size, and were still so on the thirteenth. Glands down the neck were also greatly enlarged. In groin they were so enlarged as to be visible. The enlargement commenced on the second and declined on the fifth.

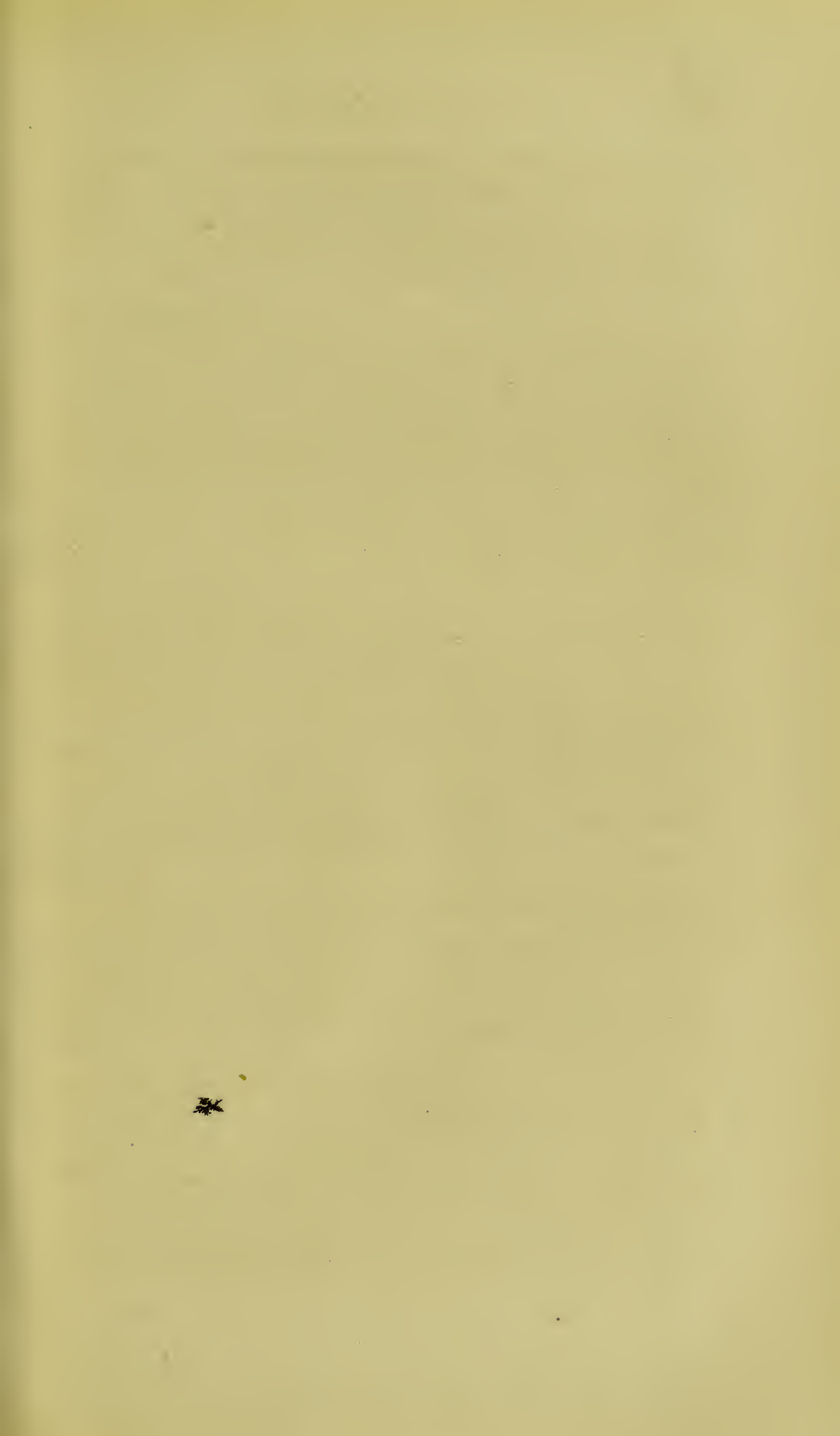
Tongue thickly furred on the second; this cleared off, and left the strawberry tongue on the fourth; this continued till the eighth inclusive; the papillæ then became less prominent, but on the fourteenth tongue was still beefy.

Fauces, &c., very red and much swollen, from the second to fourth inclusive; this was still more marked from the fifth to seventh; on the latter day the parts were very much more red and swollen. On the eighth the redness and swelling began to decline, and the parts were covered with muco-purulent-looking matter. On the thirteenth day they were still swollen and red.

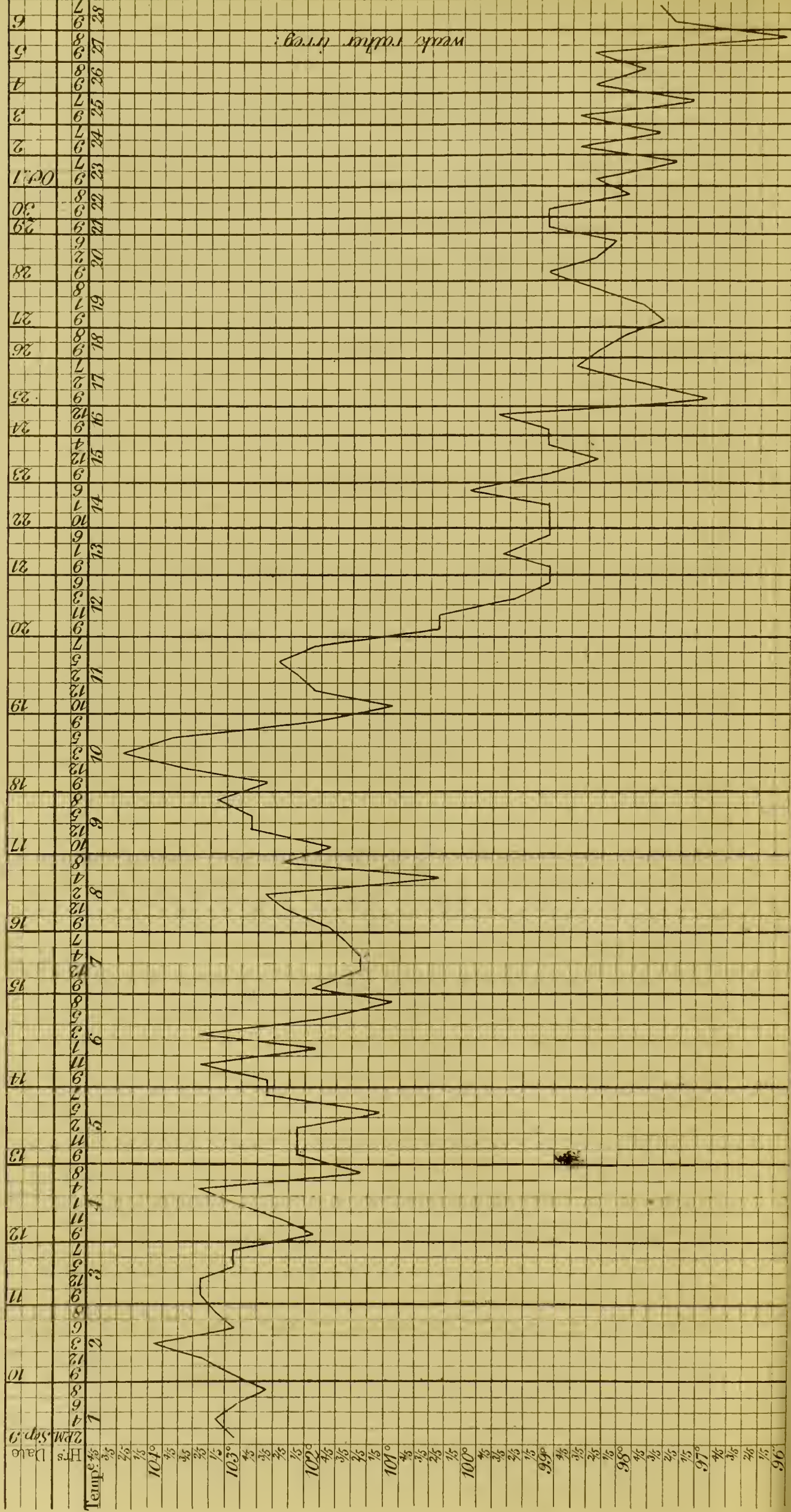
Abundance of sudamina were observed on the chest and abdomen on the second day.

Appetite was rather bad on the fourth day; after this it slowly improved till the eighth day, when it was again bad, but improved on the thirteenth.

The child throughout was in a very low condition. Lips were dry from the first; alæ of nose became red and exco-



Case 22. Margaret Peacock. $\text{Æt } 5\frac{1}{2}$



riated on the sixth, and continued so throughout. Lips were greatly swollen, cracked, and bleeding, on the ninth day; on the fifteenth they were better.

Bowels.—From the fifth to the ninth had three or four liquid motions daily; on the fourteenth day the motions were less frequent.

Child died suddenly on the night of the sixteenth.

Post-mortem.—The lymphatic glands generally of the body were loaded with tubercle, and the small intestines extensively ulcerated. There was old cretified tubercle in the lungs; none of recent origin.

Temperature.—On the second day it rose to $103\frac{2}{5}$; on the third, to $104\frac{3}{5}$; on the fourth, to $103\frac{4}{5}$; on the fifth, to $103\frac{3}{5}$; on the sixth, to $102\frac{3}{5}$; on the seventh, to $102\frac{4}{5}$; on the eighth, to $102\frac{2}{5}$; on the ninth, to 103 ; on the tenth, to $103\frac{2}{5}$; on the eleventh, to 104 ; on the twelfth, to $103\frac{3}{5}$; on the thirteenth, $102\frac{1}{5}$; on the fourteenth, $101\frac{2}{5}$; on the fifteenth, $101\frac{2}{5}$; on the sixteenth, $101\frac{2}{5}$.

CASE 22 (see Diagram 7).—Margaret Peacock, æt. $5\frac{1}{2}$. Seized at 1 a.m., September 9th. Rash appeared on the same day. She first complained of sore throat on September 2nd, but remained in her usual health till the 9th. Rash was universal on the first, and disappeared on the fifth day.

Desquamation began on the chest, abdomen, and arms on the twelfth day; began on the legs on the sixteenth, and on the same day was completed on the chest; ceased on the abdomen and legs between the twentieth and twenty-seventh days, and still continued on the hands on the twenty-seventh.

Alæ of nose in this case were excoriated.

Conjunctivæ injected from the first to third day inclusive.

Lips were dry and covered with sordes from the first to twelfth day inclusive.

Glands at the angles of the jaw were enlarged on the first, and continued so to the ninth. On the tenth and twelfth the swelling had increased greatly, extending on the

face over the parotid gland; on the thirteenth it began to diminish, but continued to be enlarged even on the twenty-seventh. Glands in groin were enlarged on the sixteenth day; after this no note of their condition was made.

Tongue, rather furred on the first; fur cleared off, but left the tongue dry and brown, on the third; remained so and was cracked till the eleventh day inclusive; on the thirteenth it was moister; on the sixteenth was clean, continuing so afterwards.

Fauces, &c., red and covered with mucus on the first and third; were still redder on the fourth. Redness was less, but swelling more, on the fifth to ninth inclusive; the parts then improved, and were normal on the sixteenth.

Body covered with sudamina on the ninth. Appetite improved on the ninth day.

Lungs healthy throughout.

Heart was healthy on the ninth. No note was made after this till the eleventh, when a distinct murmur was caught, audible at base and apex, most so at the base. It became much less distinct at the apex on the twelfth; the murmur continued throughout.

Never any albumen in her urine.

Child continued very poorly till the ninth day, when she improved, and continued from this time to mend.

CASE 23.—Sophia Pattenson, æt. 5½. On September 12th, after tea, she was seized with vomiting and pain in the head. On September 13th the rash appeared; was universal. According to the mother, it declined on the 15th September (fourth day). It disappeared from the whole body on the seventh.

Desquamation began on the face on the seventh; on the chest and abdomen on the eighth; on the legs between the thirteenth and seventeenth days; on the palms on the tenth; was very active on the chest, abdomen, and the arms, on the seventeenth, and was completed on the twenty-first; still continues on the legs and hands on the twenty-fourth day.

Glands at the angles of the jaw were normal till the ninth day, when they became swollen and very painful on the left

side; they decreased in size from the eleventh, but still remained much enlarged on the seventeenth day. Glands in groin were enlarged on the fifth day, and resumed their normal size between the thirteenth and twenty-first days.

Tongue clean throughout.

Throat normal throughout.

Appetite was middling on the sixth day, and improved after this.

Lungs always healthy.

Heart.—A distinct systolic murmur, audible at base and apex, on the eighth; ceased at the apex but continued audible at the base, and was inaudible at either cartilage from the ninth to the thirteenth inclusive. No murmur was audible on the seventeenth nor twenty-first day. No notes were taken in the intermediate days.

No albumen in the urine at any time.

The child was cheerful on the fifth; on the sixth became heavy, drowsy, and fretful, passed a restless night on the eighth. After the ninth day she improved again rapidly.

Temperature.—On the fifth day it reached 100; on the sixth, $99\frac{2}{5}$; seventh, $99\frac{1}{5}$; eighth, $104\frac{1}{5}$; ninth, $103\frac{1}{5}$; tenth, $102\frac{2}{5}$; eleventh, $102\frac{2}{5}$; twelfth, $102\frac{3}{5}$; thirteenth, 100; fourteenth, $98\frac{3}{5}$; fifteenth, $98\frac{2}{5}$. It remained at about 98 till the twenty-fifth day.

CASE 24.—Mary Hugden, æt. 11; weight, 25·5 kilogrammes. Patient was seized with sore throat on November 23rd; rash appeared on the 24th. Rash was well out and universal till the seventh day inclusive; then declined, and, on the tenth, there was a mere trace.

Desquamation began on the face on the seventh; began on the hands on the ninth; on the twelfth it was universal.

Tongue was dry and glazed on the seventh; moister, eighth and ninth.

Sweated profusely on the night of the eighth and ninth.

Appetite improved on the tenth.

Observations were then discontinued till January 22nd (sixty-first day). During this interval she had much blood

and albumen in the urine. On the sixty-first day she was very pale, scarcely any anasarca.

A small amount of albumen occurred in the urine from the sixty-third to sixty-eighth days inclusive; after this the urine was not examined.

The temperature in this case was not taken after the twelfth day; from the fifth to the twelfth days inclusive the temperature varied between 103° and 104° .

Table giving the daily amount of urea, NaCl, and urinary water.

Day of Disease.	Urea.	NaCl.	Water.
	Grammes.		
Sixth	17·550	3·565	1486 c.c.
Seventh	18·487	4·006	2175
Eighth	15·200	2·968	2375
Ninth	13·450	2·220	1850
Tenth	14·437	1·788	1875
Eleventh	14·265	1·902	1585
Twelfth	15·096	2·294	1480
Thirteenth	10·400	0·357	650
Sixty-third	6·570		595
Sixty-fourth	6·864	3·630	660
Sixty-fifth	9·086	4·543	770
Sixty-sixth	6·420		600
Sixty-seventh	5·050	2·127	370
Sixty-eighth	7·155	3·445	530

CASE 25.—Emma Walsham, height, 4 ft. $1\frac{1}{2}$ in.; weight, 23·6 kilogrammes. Sore throat noticed on April 3rd; rash appeared on the third day. She came under notice on the sixteenth day of the disease. On that day there was copious desquamation over the neck; on the eighteenth day it involved the chest, abdomen, and thighs; on the twenty-first it began on the palms of the hands; on the twenty-eighth it had ceased on the arms; on the thirty-second it was completed on the chest; also on the abdomen on the thirty-sixth. On the thirty-ninth desquamation only

observed on the feet, and here it was still continued on the forty-fourth day.

Tongue was pale, and some of the papillæ rather prominent when admitted.

The glands at the angles of the jaw reached their normal size between the twenty-ninth and thirty-ninth days. On the forty-fourth they were still shotty in the groins.

Heart and lungs healthy throughout.

On the twenty-seventh day the child was noticed to be puffy about the face (she had been up for several days); twenty-eighth, kept in bed; puffy about eye, and continued so. On the thirty-first day was very feverish, and, during the night, she was delirious.

Urine.—Seventeenth day.—No albumen.

Eighteenth.—A shade.

Nineteenth to twenty-sixth inclusive.—No albumen.

Twenty-seventh.—A shade.

Twenty-eighth.—More distinct; no blood.

Twenty-ninth.—Ditto, ditto.

Thirtieth.—Distinct cloud of albumen. Some blood detected by microscope.

Thirty-first and thirty-second.—No albumen. Some blood detected.

Thirty-fourth.—Smoky, but scarcely a trace of albumen.

Thirty-fifth.—Slightest cloud of albumen. Blood less.

Thirty-sixth.—No albumen. Blood less.

Thirty-seventh.—Slight trace of albumen. Some blood.

Thirty-ninth to forty-first inclusive. No albumen, but blood-discs seen.

From forty-second day to time of dismissal, no blood nor albumen.

Temperature.—The patient was admitted on the sixteenth day of the disease; from this date till the twenty-seventh day inclusive, it remained normal. On the twenty-eighth, it rose to 100; on the twenty-ninth, to $104\frac{2}{5}$; on the thirtieth, to $98\frac{3}{5}$; and, on the thirty-first, to $99\frac{3}{5}$. After this it continued between 98 and 99 till the forty-sixth day.

Table giving the daily amount of urea and urinary water.

Day of Disease.	Urea.	Water.
	Grammes.	
Seventeenth	7·875	750 cc.
Eighteenth.....	15·360	960
Nineteenth.....	Lost.	...
Twentieth	13·322	730
Twenty-first	12·320	880
Twenty-second ...	11·000	500
Twenty-third	12·247	710
Twenty-fourth ...	11·870	625
Twenty-fifth	14·550	430
Twenty-sixth.....	13·120	410
Twenty-seventh...	12·905	445
Twenty-eighth ...	12·200	610
Twenty-ninth.....	11·560	680
Thirtieth	11·505	885
Thirty-first.....	13·037	745
Thirty-second ...	9·955	610
Thirty-third	11·407	585
Thirty-fourth.....	12·800	800
Thirty-fifth	10·406	925
Thirty-sixth	14·899	908
Thirty-seventh ...	13·680	1140
Thirty-eighth.....	12·325	850
Thirty-ninth	14·700	700
Fortieth	15·505	585
Forty-first	15·502	385
Forty-second	16·065	595
Forty-third.....	17·381	675
Forty-fourth	16·500	600
Forty-fifth	13·870	730

CASE 26 (see Diagram 8).— Mary Anne Dall, æt. 2 years 2 months, was first seized at 5 p.m. of Sept. 11th. Rash appeared on the afternoon of Sept. 12th.

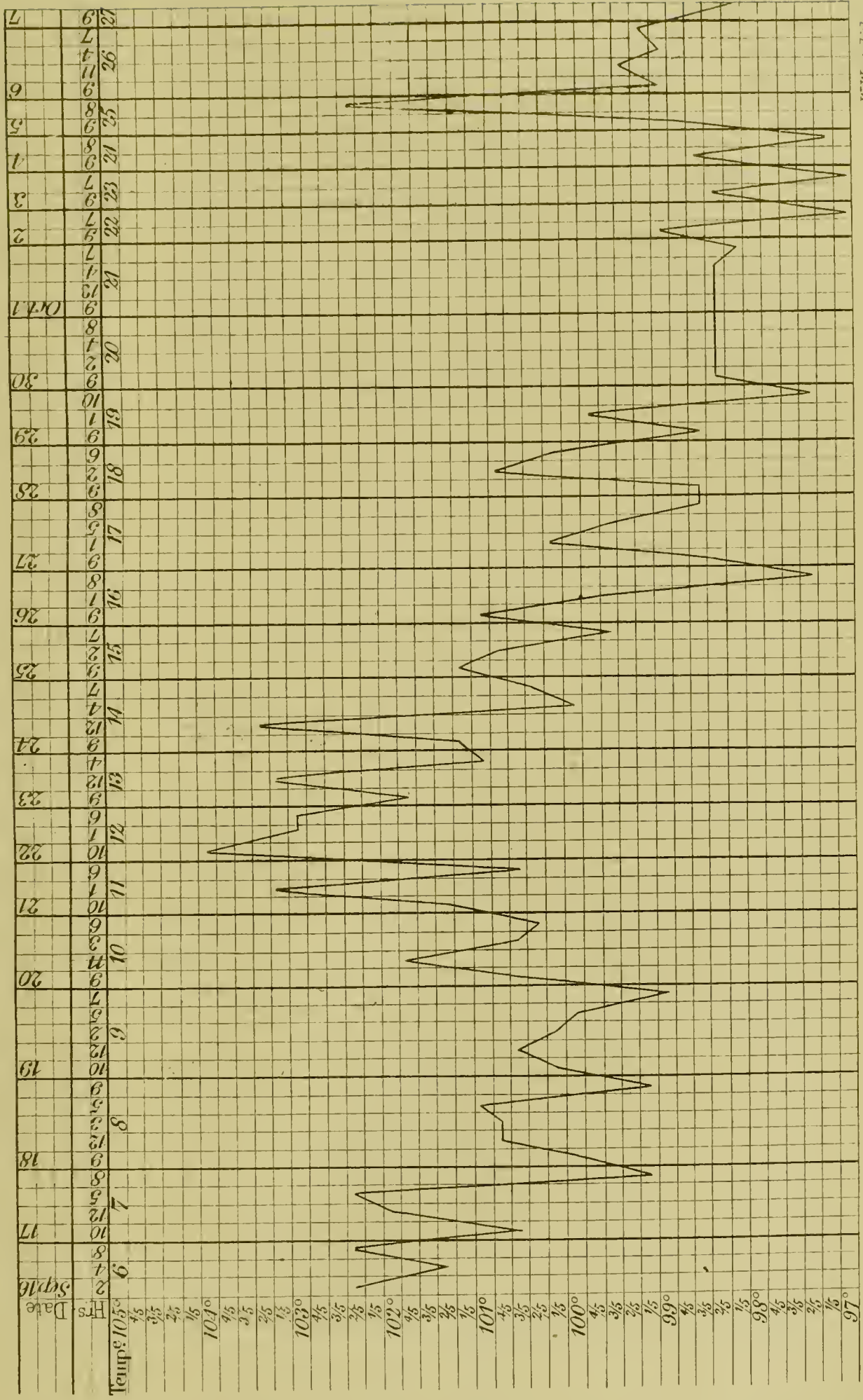
At the time of admission there was a slight rash over the whole body, papilliform ; this left the chest on the eighth day ; abdomen, leg, and arms, on the seventh.

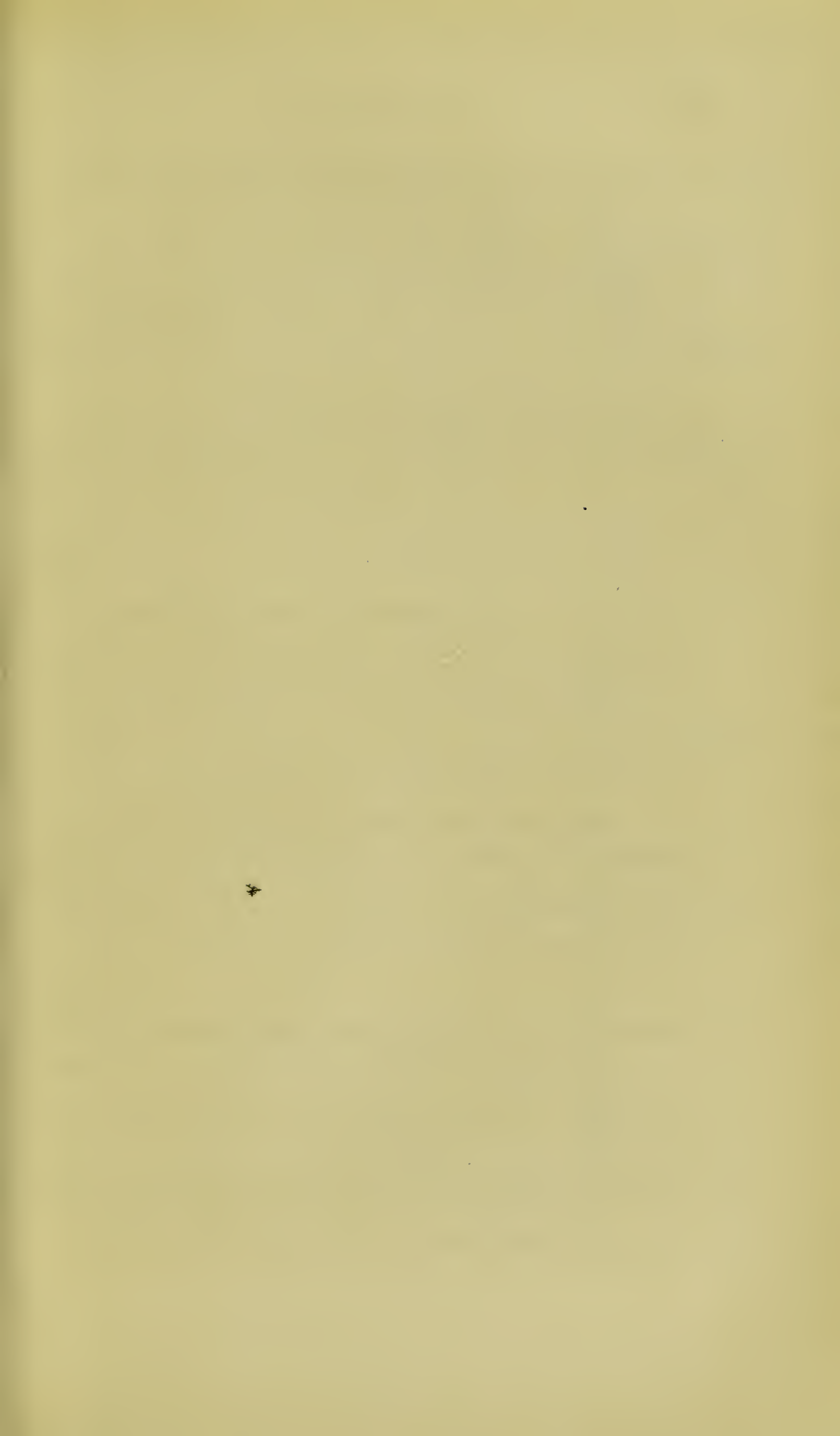
Glands at angles of jaws and groins, were slightly enlarged, till the tenth day inclusive.

The throat was red and swollen on the sixth, after this it improved, and was much better on the tenth.

Tongue was furred on the seventh, clean on the eighth day.

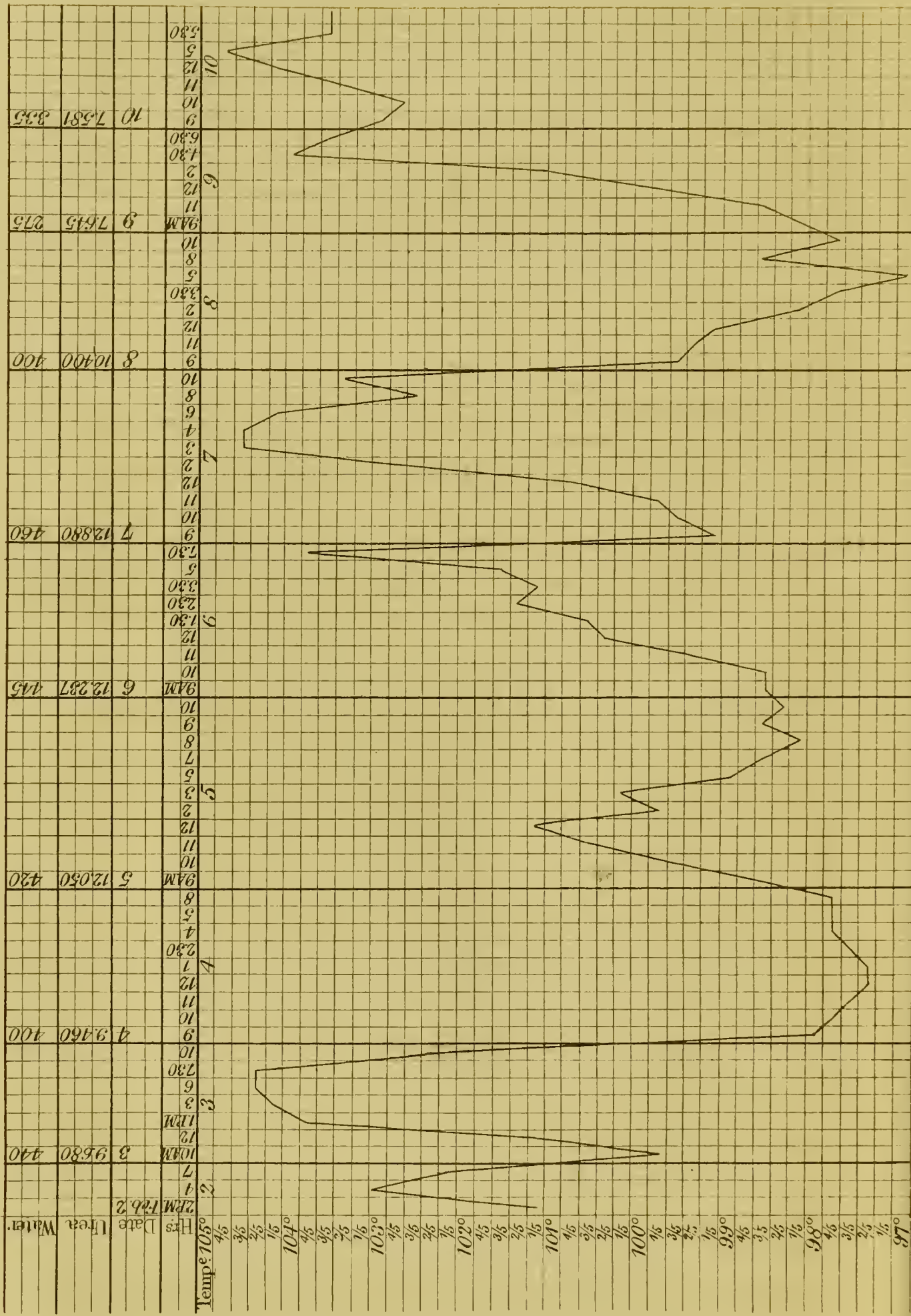
Case 26. Mary Ann Dally.





Case 29. James Kelly. At 9 years, 4 months.

No 9.



Heart and lungs were always healthy.

No albumen in the urine at any time.

CASE 27.—Mary Wright, urine never contained any albumen. Child died on the fourth day of the disease.

Temperature.—On the second day, it rose to $104\frac{4}{5}$; on the third, $104\frac{2}{5}$; on the fourth, $104\frac{2}{5}$.

CASE 28.—Mary Clarke, æt. 5 years 3 months. July 9th, in the morning the child was chilly, in the evening she complained of headache.

July 11th, rash first noticed.

Rash was strongly out over the whole body, till the sixth day inclusive, then diminished, and disappeared from the legs and arms on the eighth, and on the same day it was very slight on the rest of the body.

Miliary vesicles appeared on the fourth day, increased in quantity till the sixth inclusive, occurring on neck, chest, abdomen, and thighs. All trace of them was gone on the seventh.

Child vomited several times a grass-green coloured matter on the fourth and fifth, none on the sixth.

There was no albumen in the urine at any time. Was first delirious on the night of the fifth, this continued nightly till time of her death. She had a very putrid smell on the eighth day. Died on the eighth day.

The temperature throughout varied between 103° and 105° .

CASE 29 (see Diagram 9).—James Kelly, æt. 9 years 4 months, admitted Feb. 2nd; ill first, Jan. 27th.

Feb. 3rd.—Slept excellently; pulse much better, tongue still furred; puffy about face; legs pit slightly, very distinct cloud of albumen in urine removed by two grammes of animal charcoal. To-day he had a muco-purulent discharge from nose.

4th.—Hot air bath $\frac{3}{4}$ hour, perspired freely, albumen in

urine same, uric acid, various shapes, globular, lozenge, some casts.

5th.—Much better ; warm bath five minutes.

6th.—Wishes to get up, urine uric, no casts, albumen.

7th.—Not so well, appetite less, legs pit on pressure, very puffy about face, much more albumen in urine ; hot air bath 6 p.m., perspired greatly.

8th.—Says he feels better ; tongue thickly furred, very puffy about face and eyes, quantity of albumen in urine much increased ; hot air bath 6 p.m., *in as usual*, half an hour ; perspired freely.

9th.—Decidedly less albumen in urine, more puffy about face.

10th.—Face and legs certainly much more œdematous, nothing so well to-day ; drowsy.

12th.—Very sick ; 2·30 foamed at mouth, groaned, face distorted into numerous grimaces, passed his fæces and urine, and had twitching of arms. Fit lasted quarter of an hour ; he never became conscious, fit returned in twenty minutes.

5 p.m. Unconscious ; eyes open, foaming at mouth, groans occasionally ; hot air bath, and mustard poultice over his loins.

5·20. Another fit ; fit continued till 8 p.m. ; he died at 12·20 p.m.

OBSERVATIONS
ON
BOX (BUXUS SEMPERVIRENS),
WITH ESPECIAL REFERENCE TO THE TRUE NATURE OF
TETANUS.

BY
SYDNEY RINGER, M.D.,
PROFESSOR OF THERAPEUTICS AT UNIVERSITY COLLEGE;
AND
WILLIAM MURRELL, L.R.C.P.,
DEMONSTRATOR OF PHYSIOLOGY AT UNIVERSITY COLLEGE.

(Received May 9th—Read May 23rd, 1876.)

Introductory and Experimental.

WE were induced to commence an investigation of the physiological action of box from the reputation it has acquired in the treatment of hydrophobia, and the frequency with which it enters into the composition of nostrums having obtained a reputation for the cure of this disease.

The curious, and at first sight contradictory, phenomena observed in frogs which had been injected with box led us to deviate from our original plan, and to make the experiments here detailed in the hope of throwing some light on the true nature of tetanus.

As yet we have had but little experience of the use of

box clinically, and it is not our intention in the present communication to offer any observations as to its employment in the treatment of disease, or its value as a therapeutical agent.

All the experiments recorded in this paper were made on frogs. We used two extracts of box; one dilute, containing in each minim the active principle of one grain of the dried leaf, and a concentrated extract three times this strength. The drug was introduced under the skin in the neighbourhood of the posterior lymph hearts by means of a hypodermic syringe. In all cases where the animal survived for some hours care was taken to keep it moist, and when not actually under observation it was placed on a glass plate in a flat covered dish containing a little water.

The extract was prepared for us by Mr. Gerrard, teacher of pharmacy at University College.

We will first describe a typical case. Two minutes after the injection the frog became dull and its movements slow, and this condition increasing, in five minutes it could not turn over when laid on its back. In twenty minutes slight tetanus occurred, at first provoked only by strong stimulation, a weaker one exciting only coördinated reflex action. At first, too, though for a very short time, the tetanus was limited to the irritated limb. Soon, however, normal reflex action was entirely replaced by tetanic convulsions, and the tetanus rapidly increased, becoming severe thirty-eight minutes from the commencement of the experiment, and remained at its height for six minutes, and then rapidly declined. (So rapid indeed is the declension sometimes, that on one occasion where the paroxysm lasted three quarters of a minute, afterwards, when re-excited, the paroxysm lasted only a quarter of a minute, and after another five minutes interval only two seconds.) The tetanus continued very weak for an hour, during which time stimulation excited only a feeble tetanic paroxysm, speedily subsiding, and tetanus could not be again produced till the animal had rested awhile. As the

tetanus declined stronger irritation and a longer rest were necessary to the production of a paroxysm, whilst the attacks grew gradually feebler and feebler, till they diminished to a mere quiver of the muscles. It was evident that tetanus and paralysis were progressing together, the paralysis gradually increasing, overpowering the tetanus, and finally abolishing it.

In this case first loss of power occurred, which appeared to us more like loss of voluntary than reflex power; next, rather severe tetanus accompanied by paralysis. We had, in fact—

1. Tetanus with increased action—or strong tetanus.
2. Tetanus with depressed action—or weak tetanus.
3. Complete paralysis.

The foregoing account represents a typical experimental case, yet we met with many exceptions, the symptoms running a somewhat different course. Thus in certain cases, due as we shall show to the degree of concentration of the extract, the tetanus was very slight, so slight, indeed, that in each tetanic convulsion we think the discharge of nervous force in the cord must have been less than in a vigorous normal (coördinated) reflex act. In other instances the tetanus was still slighter, so that the nervous discharge must have been less than that in a coördinated reflex act. Here then we had simply: 1. Tetanus with depressed action. 2. Complete paralysis.

In all the cases, even when the tetanus was severe, a stage was reached when becoming no stronger than a normal reflex act, the tetanus ultimately became even weaker than a normal reflex act.

In other cases no tetanus occurred, but simply progressive paralysis, which at last became complete. These varying results were produced by the same dose of the poison in frogs of the same weight, an apparent discrepancy which our further investigations clear up. Thus a very concentrated solution of the extract excites strong tetanus, whilst the same dose diluted excites either no tetanus, or very little, as the accompanying tables exemplify. The

frogs included in the first table were injected under the skin of the back in various doses with a solution the strength of three grains of the dried leaf in one minim of water, and with two exceptions this preparation produced strong tetanus. In the *first* column we give the date; in the *second* the weight of the frog; in the *third* the dose of the extract, giving the quantities in grains of the leaf; in the *fourth* the degree of tetanus induced; in the *fifth* the time of commencement of the tetanus; in the *sixth*, the time from its commencement when the tetanus begun to decline; and in the seventh the duration of the tetanus. The table is divided into two parts, in the first part the frogs were merely poisoned, in those in the second part the cord was divided opposite the occipito-atlantal membrane, and then a peg was passed upwards into the skull, thus destroying the medulla and brain (brainless frogs).

TABLE I.—*Unmutilated frogs.*

Part 1.

Date.	Weight in grammes of frog.	Dose of leaf in form of extract.	Degree of tetanus.	Tetanus first occurred in	Tetanus began to decline from its commencement.	Duration of tetanus.
April 7	...	30 grains	Strong	13 minutes		
" 7	...	12 "	"	19 "		
" 11	38	9 "	"	22 "	35 minutes	2 h. 25 m.
" 12	...	12 "	"	27 "	16 "	
" 12	...	27 "	"	18 "	15 "	1 h. 8 m.
" 13	30	30 "	"	10 "	19 "	1 h. 8 m.
" 20	25	9 "	"	16 "	18 "	2 h. 35 m.
" 20	32	15 "	"	18 "	16 "	1 h. 20 m.
" 20	24	6 "	"	29 "	11 "	2 h.
" 20	26	9 "	"	19 "	16 "	1 h. 43 m.
" 20	19	9 "	"	16 "	17 "	1 h. 53 m.
" 20	23	9 "	"	18 "	20 "	1 h. 36 m.
Average	27*	12* grains		19 minutes	18 minutes	1 h. 45 m.

* These averages are calculated only where both weight and dose are given.

TABLE I (*continued*).—*Brainless frogs.**Part 2.*

Date.	Weight of frog in grms.	Dose of leaf in form of extract.	Degree of tetanus.	Tetanus first observed in	Tetanus began to decline from its commencement	Duration of tetanus.	Loss of reflex power preceding tetanus.
April 7	28	27 grains	Strong	16 min.	...	1 h. 37 m.	5 min.
" 7	28	27 "	"	30 "	...	1 h. 10 m.	
" 11	25	24 "	"	32 "	...	2 h. 39 m.	
" 12	...	27 "	"	24 "	...	...	
" 12	25	24 "	"	32 "	...	1 h.	
" 21	27	9 "	"	47 "	53 min.	1 h.	5 "
" 21	29	12 "	"	33 "	27 "	1 h. 30 m.	
" 21	28	12 "	"	36 "	56 "	1 h.	
" 21	27	12 "	"	40 "			10 "
" 22	22	9 "	"	26 "	29 "	1 h. 50 m.	
" 22	28	9 "	"	31 "	41 "	50 m.	
" 24	20	9 "	"	21 "	37 "	1 h. 25 m.	5 "
" 24	31	9 "	"	34 "	24 "	1 h. 21 m.	8 "
" 24	30	9 "	"	25 "	32 "	...	21 "
" 24	21	9 "	"	24 "	28 "	1 h. 10 m.	5 "
May 1	22	9 "	"	21 "	28 "	1 h. 43 m.	10 "
" 1	...	9 "	Very weak	14 "	...	...	5 "
" 1	19	9 "	Very strong	20 "	43 "	3 h.	10 "
" 1	19	9 "	Slight	25 "	...	1 h. 20 m.	10 "
" 2	27	9 "	Strong	19 "	44 "	1 h. 40 m.	8 "
Average	25	14 grains		27 min.	37 min.	1 h. 31 m.	8 min.*

* Excluding the 21 minutes, average 7 minutes.

TABLE II.—*Exemplifying the effect of the dilute extract, each minim containing the extract from one grain of the dried leaf.*

Date.	Weight of frog in grammes.	Dose equivalent to dried leaf.	Amount of tetanus.	Tetanus first appeared.	Duration of tetanus.
April 13	31	5 grains	Moderate	1 h. 15 m.	50 m.
„ 13	35.5	10 „	None		
„ 13	38	15 „	„		
„ 13	29	20 „	Slight	52 m.	1 h. 11 m.
„ 19	30	5 „	None		
„ 19	32	10 „	Slight	1 h. 33 m.	20 m.
„ 19	29	15 „	Moderate	56 m.	1 h. 35 m.
„ 19	29	20 „	None		
„ 19	30	10 „	Moderate	39 m.	1 h. 50 m.
„ 19	34	10 „	None		
„ 19	30	13 „	„		
„ 20	26	9 „	Very slight	1 h. 26 m.	10 m.
„ 20	21	15 „	None		
„ 20	24	6 „	„		
„ 20	30	9 „	Very slight	57 m.	1 h. 5 m.
Average	29	11 grains		1 h. 16 m.	1 h.

In the fifteen cases in the last table, in eight no tetanus occurred, moderate tetanus in three, and very slight tetanus in four. The dilute solution produced generally very slight tetanus, each paroxysm being, so far as we could estimate, weaker than a normal (coördinated) reflex act, and in several cases much weaker.

In the second table in every instance almost complete loss of voluntary and reflex power preceded the onset of the tetanus; indeed in two cases the paralysis was complete before the tetanus set in.

We suggest that the difference in the effect produced by the two solutions is owing to the quicker absorption of the concentrated solution. Its specific gravity being greater, it will pass by the law of diffusion more quickly into the blood.

The preceding tables show that the tetanus when well marked begun on an average in 19 minutes, continued

strong 18 minutes, and then rapidly declined, lasting on an average 105 minutes. With the dilute solution, the tetanus being much slighter, it began on an average, in 27 minutes and lasted 91 minutes, (see Tables I and II for further particulars, p. 393 and 394).

As we have just said, a diluted solution induces weak or only moderately strong tetanus, which sets in much later than when fully developed by the stronger solution; moreover, great or even complete loss of voluntary and reflex power always preceded the tetanus; that in fact we get a combination of paralysis and tetanus. We offer the following explanation of these facts. In a subsequent part of this paper we shall attempt to show that in tetanus there is always diminished resistance to impressions, in the cord, and that this diminished resistance may be associated with a normal or depressed condition of the cord. In poisoning with a dilute solution absorption goes on slowly and paralysis sets in and becomes almost complete before enough of the drug has been absorbed to lessen the resistance of the cord. In other words, it requires a larger dose to diminish the resistance of the cord than to produce paralysis; hence paralysis precedes and accompanies tetanic spasms.

Does Box produce its effect through the brain, spinal cord, nerves or muscles? We shall consider these points seriatim.

Very soon after poisoning, loss of power sets in. We carefully examined in sixteen cases for the earliest evidence of loss of power and find that it varies from one to five minutes, giving an average of two minutes and a half. The quantities of the extract employed varied from five to twenty grains of the dried leaf, the average being 10·8 grains.

TABLE III.—*Showing time of onset of loss of power in frogs produced by box.*

Number of frog.	Weight of frog in grammes.	Dose of leaf in form of extract.	Strength of preparation.	Loss of power begun in
1	30	5 grains	Dilute	5 minutes
2	32	10 "	"	5 "
3	29	15 "	"	3 "
4	29	20 "	"	3 "
5	30	10 "	"	2 "
6	34	10 "	"	2 "
7	30	13 "	"	2 "
8	25	9 "	Concentrated	3 "
9	32	15 "	"	1 "
10	26	9 "	"	3 "
11	26	9 "	Dilute	1½ "
12	21	15 "	"	2 "
13	24	6 "	"	2 "
14	30	9 "	"	2 "
15	19	9 "	Concentrated	1 "
16	23	9 "	"	3½ "
Average	27.5	10.8 grains		2½ minutes

To ascertain if all or part of this loss of power is due to the action of the box on the brain or the medulla, we divided the spinal cord, opposite the occipito-atlantal membrane in fifteen frogs, and then passed a wooden peg into the skull, destroying the medulla and brain (brainless frogs). When the effects of shock had passed off, we injected under the skin of the back the concentrated solution of the extract each minim containing the extract from three grains of leaf. Tetanus first appeared in from 14 to 47 minutes, giving an average in the twenty cases of 27 minutes (see tables on pp. 393 and 394). Shortly before the onset of the tetanus, we noticed slight but distinct diminution of reflex power, so that we could foretell the occurrence of the tetanus; the loss of reflex power generally preceding the tetanus, about five minutes, though in one case there was an interval of twenty-one minutes; the average being eight minutes, or excluding the case of twenty-one minutes, the average was seven minutes. We have shown that in

unmutilated frogs, loss of power occurs in two and a half minutes; tetanus occurs on an average in nineteen minutes. Where the influence on the cord and medulla is prevented, in pegged (brainless) frogs the tetanus is preceded by loss of reflex power for seven minutes; therefore the loss of power occurring during the twelve first minutes must be due to the influence of the poison on either the brain or the medulla.

To determine whether the loss of reflex action shortly preceding the tetanus in pithed frogs is a natural decline or is due to the action of the drug, we performed some comparative experiments by poisoning each alternate frog, and watching the reflex action as the poisoned and unpoisoned frogs lay side by side. We find that in unpoisoned frogs, if the animals are kept moist, reflex action continues undiminished for thirty hours, indeed sometimes for fifty hours, and persists from fifty to a hundred hours. For further details concerning the duration of reflex action we refer our readers to the section on tetanus p. 414.

We may draw attention here to one fact connected with the duration of reflex action in brainless frogs, which explains we think the variable effects of box and gelseminum on the cord. Thus, in some instances reflex action had ceased in 23 hours, whilst in others it lasted for 90 to 100 hours. There must be therefore naturally considerable differences in the condition of the cord, and hence the cord in one frog will be quickly and easily paralysed, whilst another may require a larger dose and a longer time.

In brainless frogs we found that box produced tetanus, preceded for a short time, as we have said, by diminution of reflex power, which further diminishing at last becomes complete. This loss of reflex power and tetanus must depend on the effect of the drug, either on the cord, nerves, or muscles. It will be convenient to treat separately of tetanus and paralysis.

Tetanus is certainly due to the action of the drug on the spinal cord for—1. There is no example of the induc-

tion of tetanus through the nerves or muscles. 2. If before poisoning, the abdominal aorta or one iliac is tied, thus protecting from the action of the poison the part below the ligature, yet these parts become tetanised as strongly as those subjected to the direct action of the poison. We proved this by eleven experiments; four times we tied the abdominal aorta, and seven times one iliac artery, verifying by post-mortem examination the efficiency of the ligatures. 3. If the sciatic nerve is divided, the other structures being left intact, the muscles of the extremity with the divided nerve are not tetanised. We verified this statement by three experiments, two on frogs, one on a toad. In each animal we divided the sciatic nerve of the left leg, and then injected under the skin of the back four minims of the stronger extract of box. In about fifteen to seventeen minutes, tetanus set in, which did not involve the muscles of the leg and foot of the left extremity, though some of the thigh muscles were affected. Irritation of the left leg failed to excite a paroxysm of tetanus.

Box likewise paralyses the reflex function of the cord. To prove this we experimented on four frogs, by tying the abdominal aorta and then poisoning the animal by injecting under the skin of the back three minims of the concentrated solution (equal to nine grains of leaf). The lower extremities were thus, of course, effectually protected from the action of the poison, and yet paralysis progressed just as in frogs, unprotected by a ligatured aorta. The following table shows the result of these experiments.

Date.	Weight of frog in grammes.	Dose.	Paralysis.	Tetanus.	First appeared.	Tetanus lasted
April 10	30	6 grains	Complete	Strong	33 min.	48 min.
May 1	25	9 "	"	"	16 "	87 "
" 1	20	9 "	"	Very slight		
" 1	19	9 "	"	None		
Average	23	8 grains			24 min.	67 min.

That both tetanus and paralysis are produced by the action of the drug on the cord is proved in our experiments regarding the influence of box on the motor nerves. In these experiments, seven in number, we tied one iliac artery, and then poisoned the animal, and in every instance save one, paralysis as complete, and tetanus as strong, seized the ligatured and protected as well as the unligatured and unprotected leg. As the muscles and motor nerves were protected by ligature, it is evident that the paralysis was not due to the action of the drug on these structures.

It is well known that some drugs as calabar bean, which paralyse through their action on the spinal cord, do likewise to a slight extent paralyse the motor nerves. Box we conclude does not affect either the motor nerves or the muscles; for did it in any degree paralyse these structures, then on tying one iliac artery before poisoning, and thus protecting the nerves and muscles of one limb from the poisoned blood, tetanus should be more marked in the protected, and paralysis should progress more rapidly in the unprotected limb. For the poison depressing the motor nerve of the unligatured limb would diminish its conducting power, and hence lessen the tetanic contractions of its muscles. This is well exemplified by slightly pressing or stretching the nerves of one leg, when the muscles of that leg are less powerfully contracted during the tetanic spasm. Moreover, if box affects either the motor nerves or muscles the paralysis in

the unprotected would progress more rapidly than in the protected leg. Again, if box affects either the nerves or muscles before the spinal cord, then loss of reflex action should occur earlier in the unprotected than in the protected limb. Now, we find as the result of seven observations given in the subjoined table, in which one iliac artery was tied, that with only one readily explicable exception, tetanus was equally well marked, that paralysis progressed equally, and was complete at the same time in both legs; moreover, the loss of reflex action begun simultaneously in both legs.

Table showing comparative amount of tetanus and paralysis in the legs produced by box after ligature of the iliac arteries.

Experiment	Date.	Weight of frog.	Dose of extract.	Proportion of dose to weight of frog.	Vessels tied.	Result.
XXXIV	1876. April 25	Grms. 76	Grains. 30	...	Lt. iliac	Tetanus less in left leg than in right
XXXV	„ 25	65	27	...	Rt. iliac	Tetanus slightly less in left leg than in right
XXXVI	„ 26	25	9	...	„	Tetanus equal
LV	May 2	24	12	...	„	Tetanus equal; loss of reflex action equal
LVI	„ 2	25	12	...	„	Tetanus equal; reflex action slightly greater in right leg
LVII	„ 2	22	12	...	„	Tetanus equal; reflex action slightly greater in right leg before injection; subsequently no difference could be detected
LVIII	„ 2	19	9	...	„	Tetanus equal; reflex action equal in both legs
Average		38	14	...		

In the last column we compare the amount of tetanus and paralysis in the protected and unprotected limbs.

This table shows that in seven frogs operated on successfully, one only exhibited any excess of tetanus, though slight, in the protected limb.

It appears then, as we have already stated, that box exerts no influence on the motor nerves or muscles. In the exceptional case just mentioned, it happened in the course of the operation, that a slight injury was inflicted on one of the abdominal nerves, thus impairing its conductivity and readily accounting for the predominance of tetanus in the limb with its uninjured nerve.

In all our operations on the abdominal vessels, we took every care to avoid stretching or even touching the adjacent nerves, but occasionally they lay in such close contact with the artery that it was extremely difficult to avoid injuring them.

With the view, however, of setting this question beyond the possibility of doubt we performed eight additional experiments, in which we resorted to a somewhat different mode of procedure. We will give the details of one of the most conclusive of these observations. We tied the right iliac artery of a large male German frog weighing sixty-five grammes. Fortunately very little blood was lost, and the animal seemed but little affected by the operation, jumping about actively on being released. An injection of extract of box equivalent to twenty-seven grains of the dried leaf was then administered in the neighbourhood of the posterior lymph hearts, care being taken that none of the fluid escaped through the incision made for the operation. Tetanus and paralysis were produced in due course, but into the details of these phenomena we need not now enter. Fifty minutes after the administration of the drug, when the paralysis was complete, and the tetanus had entirely ceased, the thighs were opened and the sciatic nerves exposed. A piece of very thin flat glass was then passed under each nerve so as to completely isolate; they were stimulated with a

pair of electrodes in connection with a Du Bois Reymond's induction coil, and a one-celled Daniell's battery, every care being taken to apply the excitor to each nerve in exactly the same manner and under identically the same conditions. We occasionally used a powerful shock, but as a rule we worked with the current of minimum intensity just adequate to produce the slightest perceptible quiver in the muscles to which the nerves were distributed.

It would be wearying and unprofitable to give the actual details of each single observation. We compared the condition of the nerves as regards excitability twenty-five times during a period of a little over four hours, and were unable in any instance to detect the slightest difference in their excitability.

This case alone would, we venture to think, prove conclusively that box exerts absolutely no influence on the motor nerves. There are in addition six other cases in which we successfully tied one iliac artery, and in these the most careful observation failed to detect the existence of even the slightest or most transitory difference in the condition of the nerves.

An examination of the accompanying table will show at a glance the results obtained in this series of experiments. In the first and second cases we made a considerable number of comparative observations, so as thoroughly to satisfy ourselves as to the correctness of our conclusions, but the actual number was not noted.

Table showing condition of sciatic nerves in frogs poisoned by box after ligature of one of the iliacs.

No. of experiment.	Date.	Weight of frog.	Vessels tied.	Grns. injected	Relation of dose to weight of animal.	Time of observation after injection.	No. of comparative observations.	Result.
	1876.	Grms.						
I	Ap. 12	34	R. iliac	9	...	1 h. 41 m.	?	No difference
II	" 12	30	"	5	...	1½ h.	?	"
III	" 25	65	"	27	...	1 h.	2	"
						1 h. 5 m.	2	"
						1 h. 10 m.	3	"
						1 h. 15 m.	1	"
						1 h. 20 m.	3	"
						1 h. 30 m.	1	"
						1 h. 45 m.	3	"
						2 h.	1	"
						2 h. 30 m.	3	"
						2 h. 45 m.	1	"
						3 h. 10 m.	2	"
						3 h. 30 m.	1	"
						4 h.	1	"
						4 h. 10 m.	1	"
IV	" 26	25	"	9	...	9 h. 40 m.	13	"
V	May 2	24	"	12	...	4 h.	Many	The right sciatic nerve conducts better than the left, although the difference is slight
						5 h.	7	The right nerve still acts better than the left
VI	" 2	25	"	12	...	6 h.	6	No difference
VII	" 2	22	"	12	...	2 h.	10	"
VIII	" 2	19	"	9	...	1 h.	8	"

In one instance there was a decided difference in the excitability of the two sciatics, the nerve of the protected limb acting distinctly more energetically than that of the other. What value are we to attach to this exceptional result? In answer to this question we cannot do better than detail another experiment in which the operation for ligature of the iliac artery was performed. The box was given as usual, and immediately after the decline of the tetanus and the occurrence of complete paralysis the

two sciatic nerves were exposed and an investigation was made of their power of conducting electrical stimuli as measured by the contractions of the muscles of the limb. The excitability exhibited by the nerve of the left leg was clearly greater than that of the right. The observation was made several times with varying strengths of current, and the result was in every case the same. At the post-mortem examination it was found that neither iliac artery had been tied!

This experiment demonstrates the fact that occasionally a difference normally exists in the relative activity of the two sciatic nerves. It may, we think, be fairly concluded that our exceptional case belongs to this category, and that the difference in the condition of the two nerves would have been equally apparent had we resorted to no operative procedure and had left the arteries intact.

Does box in any degree affect the muscles? In the experiments just detailed we tested the muscles of the opposite legs, the muscles of one extremity being protected from the action of the poisoned blood by ligature of its artery. The apparatus used to stimulate the muscles was that employed in the investigation of the motor nerves. The electrodes, however, were placed in actual contact with the muscular tissue. The general mode of procedure was in both investigations identical. In no instance were we able to discriminate the slightest difference either in the strength or the rapidity of contraction of the corresponding muscles of the two limbs. We conclude therefore that box exerts no direct influence on the muscular tissue.

We next proceeded to ascertain whether box poisons the afferent nerves, for if this drug had induced depression of these nerves, before the cord became tetanised, this condition would throw light on the paralysis preceding tetanus, for the depressed afferent nerves would convey to the cord a weaker impression, and the reflex acts would consequently be weaker. We find that the afferent nerves are not paralysed by box, and we base this conclu-

sion on the following experiment. After tying the iliac artery of one leg and then poisoning the animal by injecting the drug under the skin of the back, we tested reflex action in both posterior extremities by holding the animal by its toes, and we found always that reflex function remained equally good in both legs. Now, if the drug poisons the afferent nerves the impressions conveyed along the poisoned limb should then be less active than those passing through the unpoisoned limb, and reflex action in place of remaining unaffected should be less perfect when the animal is suspended by the poisoned extremity. The foregoing experiment, however, being insufficiently delicate to settle this important question, we sought more convincing evidence, and four times we repeated the following experiments. We divided the cord just below the medulla, and then destroyed the medulla and brain by passing a wooden peg into the cavity of the skull. We then tied one iliac artery carefully, closing the wound with ligatures. We next determined the weakest induction currents capable of exciting reflex action in either hind leg, and then injected under the skin of the back four minims of the concentrated extract of box. Every three or five minutes we tested the weakest currents adequate to excite reflex action in the posterior legs. As the reflex function declined, the same strength of currents would still excite in each limb an equal amount of reflex action in the poisoned as in the unpoisoned limb, till the abolition of all reflex action. We conclude, therefore, that box exerts no influence on the afferent nerves.

Having thus shown that box tetanises and paralyses by its effects on the cord, and that the afferent and motor nerves and muscles are unaffected, we wish to draw particular attention to a fact several times referred to in this investigation—that in pegged frogs, when the drug cannot of course act on the brain, after the injection of the concentrated solution of the extract, tetanus is preceded for about six minutes by loss of reflex power in the cord, and that this loss is manifested even where the subse-

quent tetanic convulsions are severe, and the nervous discharge in the cord is much greater than occurs in a normal (coördinated) reflex act; hence, according to the prevailing notion, the cord is said to be excited by the medicine. Very soon after the onset of the tetanus and even before it becomes severe the coördinated reflex power of the cord rapidly declines. Thus we have first marked loss of reflex power and then strong tetanus. This apparent contradiction—this loss of coördinated reflex power preceding tetanic convulsions and persisting in the intervals of the paroxysms—might be due, we thought, to the depressing influence of the drug on the motor or afferent nerves or muscles before the excitation of tetanus in the cord; but having shown that box does not affect these structures, it is clear that the drug must first lessen reflex action in the cord and then produce tetanus, the coördinated reflex power itself meanwhile diminishing. This apparent contradiction we have attempted to reconcile in the section on tetanus.

In twelve observations with unmutilated frogs, as we have already shown, energetic tetanus lasts only a short while, beginning to decline on an average in eighteen minutes, and in ten brainless frogs on an average in thirty-nine minutes, then it grows rapidly weaker and so continuing for an hour to an hour and a half; it then ceases and all reflex action is abolished. Is this due to the natural cessation of the functions of the cord, or to exhaustion from the tetanus, or to the medicine? It is not due to the natural death of the cord, for after dividing the cord opposite the occipito-atlantal membrane we found that reflex action continues unimpaired for thirty or forty hours. (For further remarks on the persistence of reflex action after death, see the section on tetanus.)

Nor is it due to exhaustion from the tetanic convulsions, since strychnia induces far intenser tetanus, lasting several days, whilst the tetanus from box is much less severe and lasts only an hour or two and then ends in complete paralysis. The paralysis of the cord is therefore due to the direct action of the box.

Box, then, paralyses and tetanises the spinal cord. Are these results due to the action of the drug on Setschenow's reflex inhibitory centre ; in other words, is the paralysis due to stimulation or the tetanus to paralysis of this centre ? Clearly not, for both paralysis and tetanus occurred after section of the spinal cord below this centre.

The following is a summary of our conclusions :

1. Box produces loss of power by its effects either on centres of volition or on the motor centres of the brain.

2. It next depresses the reflex function of the cord.

3. It excites tetanus, the paralysis of coördinated reflex function of the cord progressing at the same time.

4. At last, by its influence on the cord, it produces complete paralysis.

5. It produces no effect on the motor and afferent nerves and the muscles.

Remarks and Observations on Tetanus.

The foregoing observations, coupled with those we published in the 'Lancet' for 1876 on gelseminum, suggest to us the following views regarding the true nature of tetanus. Tetanus is generally said to be due to stimulation of the cord, or the cord is said to be excited ; but these expressions, we venture to think, are both erroneous and misleading.

We shall first consider strychnia tetanus. Here a slight irritation will develop rigid contraction of every muscle of the body, and this paroxysm can be excited in rapid recurrence for several days. Here no doubt an excessive discharge of nervous force does take place in the cord, and hence perhaps it may be deemed correct to say—though presently we shall have occasion to question this view—that the cord is stimulated or excited. But the effects produced by strychnia are not due to mere stimulation, for in that case the normal co-ordinated reflex movements should be retained and be more vigorously performed ; this, however, does not happen, for on irritating a frog's

posterior limb, or indeed any other part, instead of inducing the usual co-ordinated movement, all the muscles of the body become rigidly contracted, and owing to the strength of the extensor muscles prevailing over that of the flexors, the hind legs, in place of being drawn up, are powerfully extended. Here then it is evident that the impression, instead of being limited to certain parts of the cord, diffuses itself through the greater part or the whole of the cord and motor tract in the brain. As every part of the cord is excited, all coöordinated action is abolished and every muscle is contracted. Thus in the case of strychnia tetanus, with increased nervous discharge, we have lessened resistance or greater diffusibility in the spinal cord.

We venture to suggest, and we trust our subsequent remarks will prove, that in the tetanus produced by poisons, this lessened resistance is the actual cause of the tetanus, and that there is in fact no excited condition of the cord; that, if the poison merely lessens resistance, then an irritation produces excessive evolution of force throughout the cord, and consequently strong tetanus; if the poison depresses the reflex function as well as the resistance, then an irritation induces slight evolution of nervous force throughout the cord, and consequently produces only weak tetanus; there is no excited condition of the cord. The correctness of this view is well shown in the tetanus excited by box, gelseminum, and jaborandi.

We shall speak first and chiefly of box. Using a concentrated solution, we find that in almost every case box excites strong tetanus, with a far greater discharge of nervous force in the cord than takes place in a normal (coöordinated) reflex act; hence it is said that the cord is excited or stimulated; but the facts we are about to adduce will, we think, show that this augmented evolution of force depends merely on lessened resistance.

After division of the cord just below the medulla through the occipito-atlantal membrane and the destruction of the medulla and brain, so as to obtain simple uncomplicated effects of box on the cord, we have shown that loss

of coördinating reflex power (cord paralysis) always preceded the tetanus by six or seven minutes. The tetanus sets in at first so slightly that only strong irritation excites it, weaker producing simply normal reflex acts; then, as the tetanus continues and grows stronger, and becomes more easily excited, co-ordinated reflex action quickly diminishes, to be at last entirely replaced by tetanic contraction; tetanus quickly grows weaker, and soon becomes very slight, so continuing often an hour or longer, and then ends in complete abolition of reflex action.

Thus we have diminution of reflex action *followed* by tetanus, the diminution becoming more evident as the tetanus increases, the tetanus being generally for a short time severe, and each paroxysm greatly in excess of a normal (coördinated) reflex act. Were tetanus due to stimulation of the cord, we should then have this singular and we think impossible combination, namely, first depression and then stimulation of the reflex function of the cord, this stimulation continuing concurrently with a rapid depression of co-ordinated reflex action.

Since box first weakens the reflex function before producing tetanus even when the tetanus is strong, it is probable that a larger dose is required to lessen resistance than to lessen the reflex function of the cord; hence, diminution of reflex function precedes tetanus. As soon as the quantity absorbed is sufficient to lessen resistance tetanus sets in, increasing in severity and in facility of reproduction as the resistance in the cord grows less.

In gelseminum poisoning always, and in many cases of box poisoning generally, when the extract is much diluted, tetanic convulsions are either not more marked than ordinary (coördinated) reflex acts, or are much weaker; that is to say, the irritation exciting tetanic spasms causes a discharge of force in the spinal cord, either no greater, and in many instances much less than is expended in a co-ordinated reflex act, estimating the amount of nervous discharge by the amount of consequent muscular contraction. In all cases of poisoning by box, even when the tetanus is strong, the paroxysms grow weaker and weaker, and at

last they fade away to a mere quivering of the muscles. In some cases indeed, even at its height, the tetanus is manifested in little more than a quivering of the muscles. If where the tetanus is strong it is deemed necessary to assume that in addition to lessened resistance there must be stimulation of the cord, we maintain that, in the instances now advanced, there can be no stimulation or heightened action of the cord, but the very opposite condition, the reflex function in many cases being much depressed. Here the stimulus evokes reflex action in a depressed cord, but through want of resistance in the cord the impression diffuses itself, and the reflex act itself, though weak, is tetanic in character; and when it is borne in mind that this weak tetanus is preceded always by some, often by great and sometimes by almost complete depression of coördinated reflex power, the foregoing view is rendered yet more probable.

Moreover, we would urge that if tetanus is due to an excited condition of the spinal cord, the course of the symptoms from box poisoning should be different from that we find it to be. In strong box tetanus, when according to the ordinary view, the cord is stimulated and excited, then as this condition subsides the tetanic movements should gradually decline and at last cease, normal reflex (coördinated) action returning; but we actually find that the tetanic movements continue, grow weaker and weaker, till at last all movement ceases and general paralysis ensues. It may be said that the tetanus exhausts the cord, and hence the convulsions grow weaker and weaker, as the cord becomes exhausted; but this objection is certainly without foundation; for the tetanus induced by box or gelseminum lasts little more than an hour, and is much less intense than strychnia tetanus, which endures several days without exhausting the cord.

The rapid abolition of reflex action is therefore due to the paralysing influence of box on the cord. It may be said that on the occurrence of paralysis the tetanus gradually declines; but were the tetanus due simply to

heightened activity of the cord, it is evident that immediately the drug begins to depress the cord tetanus should cease; for that the same substance should simultaneously stimulate and depress the same organ is inconceivable.

In these cases, where during the tetanic paroxysm the muscular contraction is not greater than occurs in a coördinated reflex act—certainly where the contraction is weaker—we must admit that the tetanus cannot depend on an excited condition of the cord, but solely on its lessened resistance, enabling an impression to diffuse itself through the greater part or the whole of the motor tract of the cord; hence all the muscles being stimulated we get tetanus.

The order in which the symptoms occur favours the view here suggested. After poisoning by box we noticed that whilst a strong irritation excited tetanus, a weak irritation produced a weakened but natural (coördinated) reflex act. The resistive power of the cord at this stage is, we submit, only slightly weakened, so that a strong impression can diffuse itself, whilst a weaker one is confined to that part of the cord naturally associated with the irritated nerve. At first, too, the tetanus is limited to the irritated limb because the resistive power being only a little weakened, the diffusion of the impression through the cord is correspondingly limited. Then as poisoning progresses, the resistive power of the cord grows weaker and weaker, and impressions diffuse themselves more easily and more widely, till at last the whole or the greater part of the body becomes tetanised.

In making certain observations to ascertain how long in frogs reflex action continues after section of the cord, we obtained some curious and unexpected results, which strikingly confirm the view we have ventured to advance. After dividing the cord and destroying the brain by passing a wooden peg through the occipital foramen into the cavity of the skull, we allowed time for the animal to recover from the shock, and then tested the reflex irritability. This was always natural (coördinated), and

unless the blows over the back were too frequently repeated, never in any case tetanic. We afterwards tested reflex action always thrice daily, morning, noon, and at night.

Soon after coördinated reflex action began to decline, we noticed that these frogs when allowed to fall the height of an inch or two on to the glass plate became slightly tetanic. The tetanic movements were still more manifestly induced by striking the animal with the handle of the forceps over the spine between the forelegs. In the ratio of the loss of natural (coördinated) reflex action these tetanic spasms became more marked, and were more easily produced; then as coördinated reflex action further declined, so did the tetanus; but even then, after all co-ordinated reflex action had ceased, a sharp blow over the spine or on one of the extremities would elicit slight tetanic extension of the legs, with much quivering of the abdominal muscles. We made careful observations on twenty-eight frogs, and with one exception these became tetanic.

We will now describe in detail one of our ordinary cases of tetanus, taking for the purpose the first on the list. The animal was a common English frog weighing eighteen grammes. The experiment was commenced on Friday the 28th of April, the weather at the time being warm and showery.

The head of the animal having been depressed with the forefinger of the left hand, the nail readily detected the depression at the base of the skull. The point of a clean, sharp knife was then introduced so as to cut through the occipito-atlantal membrane and the subjacent medulla. The extremity of a sharpened match was then thrust into the skull through the foramen magnum so as to destroy the brain with as little loss of blood as possible. The spigot of wood was retained in position, and no hæmorrhage was visible externally. The animal suffered but slightly from the shock, and in a minute or two reflex action was found to be perfect, the whole body being drawn up when lifted by one leg. Twenty-one hours after, on striking the back in the cervical region with a pair of forceps, the legs were suddenly shot out straight, in a manner which was clearly tetanic in nature. On placing side by side with this animal a frog which had just been operated on, the contrast was very great, the legs

in the latter remaining perfectly motionless when the back was struck. By the evening of the second day (thirty hours after the operation) there was a little diminution of reflex action. At first, on striking the back no tetanus was observed, but on repeating the blow the legs were shot out as in the morning, but rather more strongly. On Sunday morning (forty-five and a half hours after the operation) a still further decline in the amount of coördinated reflex action was noticeable, although it was still fairly strong. The tetanus had increased in severity and was very readily excited. Lifting the animal ever so slightly from the table and then dropping it would at once induce a paroxysm, the legs being shot out and the web of the foot widely distended. On Monday both reflex action and tetanus gradually declined; and on Tuesday (the fifth day) had entirely ceased.

We will now describe an experiment in which the tetanus may we venture to think, be fairly denominated "very strong." There is no occasion to describe the mode of preparation, as it was identical with that already detailed. It was thought possible that the rapidity of decomposition in the warm laboratory might interfere with the development or duration of tetanus, and this animal was consequently kept during the time it was under observation in what we may call a miniature icehouse, the temperature of which ranged from 12° to 15° C. Four hours after the operation coördinated reflex action was good, and there was slight tetanus. During the remainder of this and on the following day the tetanus gradually increased in intensity, and in thirty-one hours after the operation was very powerful. The slightest touch on the back induced a violent tetanic spasm, in which the legs were forcibly extended. The paroxysm lasted more than a minute, and the animal was taken up by the legs and held out horizontally, so great was the rigidity. The individual muscles of the limbs stood out most prominently, and as the paroxysm declined could be seen rapidly alternately contracting and relaxing. This observation was at six in the evening, and at half past seven on the following morning both tetanus and coördinated reflex action had entirely ceased.

We introduce the results of our observations in the following table. In the first column we give the number of frog; in the second the date; in the third the degree of tetanus; in the fourth the time the tetanus began on merely striking the back once or twice (more frequent and more powerful irritation would always, as we have subsequently shown, depress the cord and produce tetaniform movements); in the fifth the time the tetanus

ceased; in the sixth the time it lasted; in the seventh the time normal (coördinated) reflex action ceased.

Table comparing reflex action and tetanus in frogs which had been pegged.

No. of frog.	Date.	Tetanus, degree of.	Tetanus began.	Tetanus ceased.	Tetanus lasted.	Reflex action ceased.
	1876.		Hours	Hours	Hours	Hours
I	April 28	Moderate	30	78	48	98
II	"	Slight	20	45	25	19
III	"	"	30	78	48	52
IV	"	"	20	46	26	30
V	"	Moderate	20	98	78	78
VI	"	Strong	20	69	49	52
VII	April 29	Slight	10	49	39	57
VIII	May 3	Strong	7	79	72	79
IX	"	"	3	75	72	75
X	"	Very strong	3	55	52	55
XI	May 6	Slight	20	75	55	95
XII	"	"	20	51	31	92
XIII	"	"	20	28	8	28
XIV	"	Moderate	20	71	51	68
XV	"	"	20	71	51	68
XVI	"	"	3	68	65	68
XVII	May 10	Strong	28	51	23	51
XVIII	"	Slight	48	81	33	81
XIX	"	Very strong	28	96	68	72
XX	"	Moderate	23	106	83	96
XXI	"	None	...	...	...	23
XXII	"	Very strong	4	47	43	47
XXIII	May 15	"	4	81	77	77
XXIV	"	Strong	4	57	53	48
XXV	"	Slight	4	72	68	72
XXVI	"	Moderate	4	59	55	28
XXVII	"	Strong	4	48	44	48
XXVIII	"	Moderate	4	52	48	48

This table shows that in four frogs the tetanus was very strong; in six strong; in eight moderate; in nine slight; and in one it was absent.

The degree of tetanus varied much, generally it consisted of the posterior legs being strongly shot out, to be immediately relaxed, but with several frogs the paroxysms when at their height, lasted from a quarter of a minute to a minute, the legs being rigidly extended, so

as to raise the animal off the table, and we could hold it out horizontally by the hind legs.

We may repeat, that directly after recovery from the shock after division of the cord, even strong irritation, unless often repeated, failed to excite tetanus, but soon after, sometimes before, normal reflex action had declined, strong irritation induced tetanus, whilst weaker irritation provoked only a coördinated reflex act. As paralysis progressed, shown in the increased weakness of the coördinated reflex acts, tetanus was more readily induced and became more marked, though even at its height the paroxysms could not be induced in rapid succession, an interval of rest being required. It will be observed that in these frogs the tetanus generally closely corresponded to the latter stages of tetanus induced by box and the whole tetanic stage of gelseminum. In some cases, however, the tetanus was strongly marked, each paroxysm lasting half a minute or even longer. These cases are comparable with the whole stage of box poisoning; for in each strong paroxysm a far greater discharge of nervous force took place in the cord than occurs in a normal (coördinated) vigorous reflex act; and therefore, according to the current views, the cord would be said to be excited. But we have pointed out that tetanus was at its height simultaneously with much weakened, coördinated reflex action, and shortly before all reflex action ceased, so that when tetanus became marked we could foretel that the cord was rapidly losing power, and that soon both coördinated and tetanic reflex action would be abolished. The duration of the tetanus varied in different frogs, corresponding to the time of continuance of normal reflex action, for though after its extinction a strong slap on the back would induce slight tetanic extension of the legs, yet this soon afterwards ceased.

It may be urged that the term tetanus is not applicable to these movements excited in brainless frogs. These movements are, however, certainly tetanic; they exhibit the character of tetanic movements, though less severe than those due to many poisons. On some occasions we obtained

even strong tetanus, though never approaching in severity the powerful paroxysms induced by strychnia. With the hind limbs rigidly and tonically extended the animal could be held out horizontally. After the paroxysm declined the contraction in each muscle became clonic, and thus produced jerking extension of the legs. The paroxysm sometimes continued from half a minute to a minute; the tetanus, it is true, in these cases was unusually well marked, whilst in most of our observations the attacks were much milder, though in character still clearly tetanic, and like the declining tetanus in box and the tetanus of gelseminum. If it be objected that where the paroxysms are not severe it is not true tetanus, which we get after poisoning by box, we answer, that the weaker succeed powerful and undoubted tetanic paroxysms, these gradually growing less and less, pass insensibly into a weaker and weaker form. If, then, the weaker paroxysms after box are certainly tetanic, we are clearly justified in classing as tetanic the movements just described in brainless frogs.

This tetanus, like other forms of tetanus, depends on the spinal cord. This we proved by the following experiment:—On the occurrence of tetanus we divided the sciatic nerve of one leg, and then found that whilst in the intact leg we could readily induce tetanus, we failed to excite it in the leg with the severed nerve, though some movement occurred in the thigh muscles which receive branches above the point of division of the sciatic.

It cannot be maintained, we think, that this tetanus is due to an exalted or excited condition of the spinal cord. The tetanus is preceded by loss of reflex action; it increases in strength as the coördinated reflex action grows less; it is most marked a short time before all coördinated reflex action ceases. Like the lessened coördinated reflex action it must be due, we believe, to depression of the cord. We explain the tetanus in these brainless frogs as we explained it when occurring in the experiments with box and gelseminum. Thus, soon after death, the cord becomes depressed, and consequently reflex action becomes

weaker; but with depression of reflex action we get also diminution of the resistive power of the cord, whereby impressions cease to be restricted to their proper portion of the cord, but spreading widely cause tetanic movements. At first, before much weakening of the resistance of the cord sets in, it requires a strong irritation to overcome the remaining resistance, weaker irritation still inducing coördinated reflex action. As depression of the cord progresses, the resistive power grows weaker, and the tetanic movements are more readily induced and are more marked. As, however, the cord is much depressed they are rarely severe, and an interval is required to permit the cord to recover from the effects of the previous discharge. The depression of reflex action and resistive power progress at the same time, and consequently the total loss of power of the cord both coördinated (natural) and tetanic contraction can be induced, the coördinated by slight, the tetanic by stronger irritation.

The following facts also tend to show that tetanus depends on a depressed condition of the spinal cord. In these brainless frogs, at a time when a strong irritation was required to excite even slight tetanus by a repetition of the strong irritation, as for instance giving sharp blows in quick succession over the upper part of the spine, the tetanus soon became much more marked, and it was observed that, after such strong irritation, normal reflex actions were induced with more difficulty. The correct interpretation of these facts, we think, is that the shock of a succession of blows depresses the cord's resistive power whereby the irritation diffusing itself more widely causes more marked tetanic movements, and at the same time weakens normal (coördinated) reflex action. If the irritation is pushed still further, the depression becomes so great as temporarily to abolish both coördinated and tetanic reflex action, and a short time is required for the cord to recover itself.

The following observation tends to show the validity of this explanation. On striking repeatedly a living vigorous

frog strongly on the back between the shoulders, we excite at first simply coördinated reflex acts, but in a short time after each blow the posterior legs are shot out in a tetanic manner, though far less energetically than when the same phenomenon occurs in brainless frogs on the decline of reflex action. The tetaniform movement occurs only when the shock of the blows has so depressed the cord that all voluntary and normal reflex action is for the time abolished. After rest the normal (coördinated) reflex action returns, and these phenomena can be re-elicited.

It appears that some agents, like strychnia, depress only the resistive power, whilst leaving unimpaired the reflex function of the cord. Hence, with the removal of the restraining influence, slight impressions diffuse themselves throughout the cord, and produce not only a general, but likewise an excessive evolution of nervous force. Other agents depress both the resistive as well as the reflex power of the cord; hence we get tetanus, though weak in character. In some cases the effects are developed more on the reflex function than on the resistive power, and here, as with gelseminum, we get considerable paralysis with slight tetanus. This happens also with regard to strong blows on the back, which depress both functions very considerably. Other agents depress the resistive power early and markedly; and in a less degree the reflex function, with box for example, we get strong tetanus with slight paralysis. These views too, we think, will throw light upon the effect of slight chemical modifications of a drug on physiological action. Nerves in their constitution must differ from one another and from the cerebral nervous system, since a given poison may affect one part only of the nervous system; for instance, the motor nerves leaving the cord unaffected. Strychnia excites powerful tetanus, and when given in very large doses simultaneously depresses the motor nerves. If converted into an ethyl compound by substituting the radicle ethyl in place of a molecule of hydrogen, strychnia no longer tetanises, but powerfully paralyses the ends of the motor nerves. We submit that

the physiological action is not entirely reversed. As strychnia it paralyses the constraining or resistive power of the cord; when converted into ethyl-strychnia, its chemical affinities being somewhat modified, it affects the motor nerves, but still it paralyses. It is not converted from a stimulant of the cord to a depressant of the motor nerves, but its chemical affinities being changed it affects the motor nerves; instead of paralysing the resistance of the cord, it paralyses the motor nerves. Its conversion into ethyl-strychnia heightens its affinities for the nerves, but lessens or destroys its affinity for that portion of the cord which restrains and localises reflex action.

ON THE

TEMPERATURE OF THE HUMAN BODY

IN HEALTH.

BY

SYDNEY RINGER, M.D.,

PROFESSOR OF THERAPEUTICS AT UNIVERSITY COLLEGE, LONDON,

AND THE LATE

ANDREW P. STUART, M.R.C.S.

PART I.

These investigations were made in order to learn how the temperature of the body comports itself in health; since to every one it must be obvious that without such knowledge it is impossible to determine with any approach to certainty what variations in the temperature are to be accepted as indications of disease.

It is necessary to state here some particulars of the manner these investigations were conducted, and of the precautions taken to avoid error.

The subjects of our observations were confined to bed during the times when the investigations, continued on some occasions for several days, were made. They were well covered with bed-clothes, and, indeed, as far as possible throughout the time they remained in bed, were kept under the same conditions, so that any alterations in their temperature could not be ascribed to any exposure, or to any variation in the temperature of the room, or to other accidental and preventible causes.

The thermometer was generally placed in the axilla, though on some occasions the temperature of the mouth under the tongue and of the rectum was noted at the same time. These observations are sufficiently numerous to enable us to say that, due care being taken and sufficient time allowed, the temperature of the axilla is always identical with that of the mouth and with that of the rectum, four to six inches above its termination.

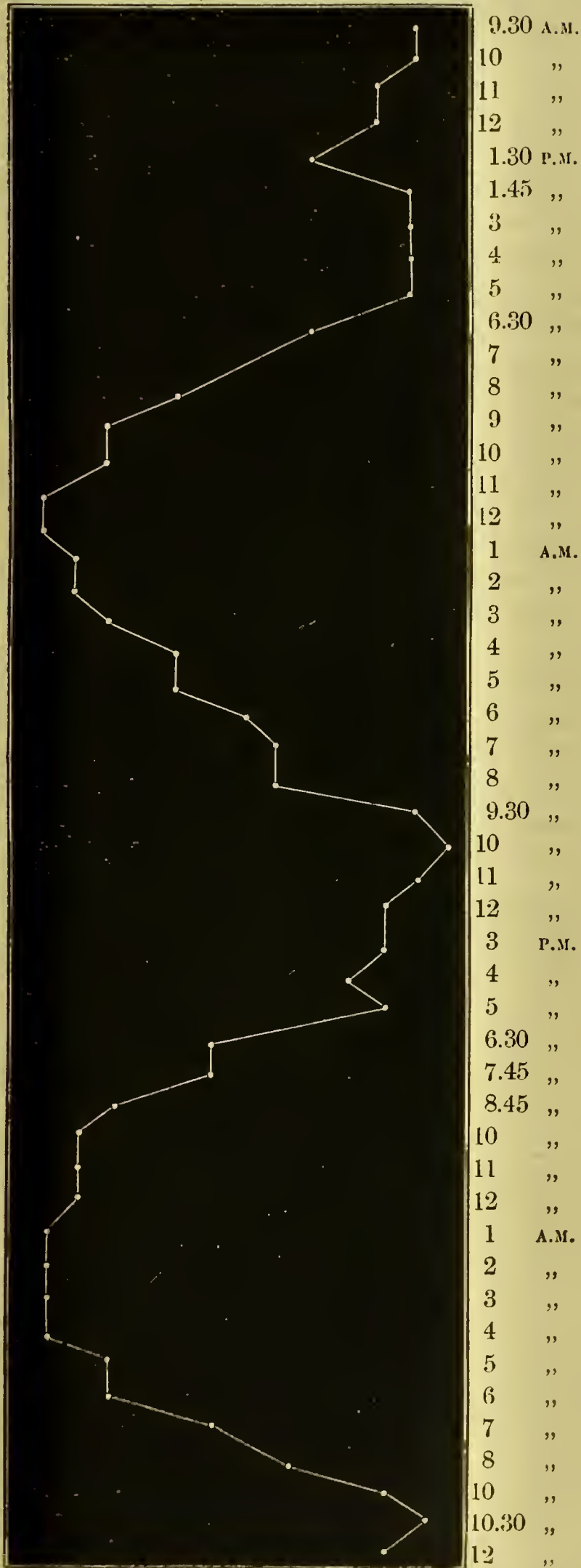
A non-registering thermometer was retained in the axilla and read *in situ* until the completion of each series of these observations; and the temperature was noted hourly, or nearly so, from 9 A.M. to a late hour in the evening, usually to 12 P.M. On some days hourly observations were made during both night and day. The time of taking food and the kind and quantity were always accurately recorded.

It is well to mention that some of the persons who were the subjects of this investigation were convalescents from various diseases, but had fairly recovered, and might be considered to be in tolerably good health.

That the subsequent remarks may be more clearly understood, we first give a short account of the general course the temperature followed in one of the boys whose case is recorded in this paper; and to render the account more intelligible, we attach a chart of his temperature variations, taken hourly for two entire days.

97°. 98°. 99°. 100°.

Chart of the Temperature of Alfred Mountain.



This chart indicates that the temperature does not remain at about the same degree throughout the day and night, but shows that a considerable diurnal variation occurs. The temperature reaches its highest point at about 9 A.M., and continues much the same during the chief part of the day; while in the evening it uniformly and greatly falls and remains at its lowest depression during several hours of the night; but subsequently, in the early morning hours, it again uniformly and quickly rises. This diurnal rise and fall constitutes the only great variations.

We now pass on to speak first of the observations, continued hourly without any intermission throughout the day and night, made on two lads, named respectively Alfred Mountain and Alfred Rundell. By adopting this plan we shall learn what conclusions we may safely draw from those less complete observations which were discontinued at 12 P.M.

Alfred Mountain was twelve years of age, of a robust build, well nourished and hearty. He had a patch of tinea decalvans, with which exception he was in perfect health.

The other lad, Alfred Rundell, thirteen years old, was of a rather delicate constitution, but he had a good appetite and was in his accustomed health.

To render our statement the more clear, and to enable our readers to judge for themselves of the correctness of the conclusions arrived at, we have thrown all the results of the observations into the form of Tables, but the details are recorded at the end of this section†.

In the first column of the following Table is given the name of the boy; in the second the time the observation lasted; in the third the maximum temperature of the day; in the fourth the amount of diurnal variation; in the fifth the hour when the evening fall began; and in the sixth column the hour of the commencement of the morning rise.

Name.	Time of Observation.	Maximum Daily Temperature.	Amount of Diurnal Variation.	Evening Fall begun.	Morning Rise begun.
Rundell.....	10 A.M. to 9 A.M.	99·2	2·2	6 P.M.	3 A.M.
Mountain	*9 " " 9 "	99·2	2·2	6 "	3 "
	*9 " " 9 "	99·4	2·4	6 "	7 "
	*9 " " 9 "	99·4	2·2	6 "	5 "
	*9 " " 8.15 P.M.	99·4	2·2	5 "	
	9 " " 9 A.M.	98·8	2·8	2 "	4 "
	9 " " 9 "	99·2	2·2	4 "	3 "
	9 " " 9 "	98·6	1·6	4 "	4 "

This Table shows the results of observations made hourly during both night and day, for eight days. On the four days denoted by an asterisk the temperature was taken continuously; thus the observations were

† The Charts are deposited for reference in the Archives.

taken hourly without any break, from 9.30 A.M. of January 12 to 8.15 of January 15.

The amount of daily variation of January 15 is estimated from the lowest temperature of the previous evening; but on all the other days the daily variation is estimated from the highest temperature of the day to the lowest of the following night.

From this Table we gain information on several points.

Maximum Temperature of the Day.

The average maximum temperature of lads of about 12 years of age is, according to our observations, 99° Fahr. Thus the highest temperature reached was on

1 day	98.6
1 „	98.8
3 days	99.2
3 „	99.4
Average.	99.1

Diurnal Variation of the Temperature.

On 1 day this was	1.6 Fahr.
3 days	2.2 „
3 „	2.4 „
1 day	2.8 „

It thus appears that the diurnal variation in the temperature of boys about 12 years of age is 2°·2 Fahr.

Time when the highest Temperature of the Day is reached.

This occurred at some period between the hours of 9 A.M. and 6 P.M. Thus on

1 day the highest temperature was at	2 P.M.
1 „	from 8 A.M. to 10 A.M.
1 „	at 10 „
1 „	„ 10 „
1 „	„ 4 P.M.

The Hour of the Day when the Evening Fall begins.

It will be subsequently more fully shown that during the early morning hours the temperature quickly rises, and then during the greater part of the day remains at about its highest point. In the evening it again quickly falls, until the lowest temperature of the day is reached. The time of day when the temperature of these lads begun to fall varied very greatly; thus on

1 day the evening fall began at	2 P.M.
2 days	4 „
3 „	5 „

8 days the evening fall began at	6 P.M.
3 " " " " 	7 "
1 day " " " 	9 "

In this Table we have not restricted ourselves to the observations continued during both day and night, but have used other observations in which the temperature was noted only till a late hour in the evening, as these, it is obvious, may be fairly used for our present purpose.

This Table proves, still more strongly than a foregoing one, that if our observations are continued till 8 P.M. our observations will include the maximum daily temperature of the day in boys of the age of these lads.

It shows also that in persons of their age the evening fall usually begins between 5 P.M. and 7 P.M.; but it likewise shows that exceptions occur, for the evening fall may begin either before or after the time stated. The fall, however, happens more frequently before than after.

The Hour when the Morning Rise begins.

This varies greatly. Thus on

4 days this began at		3 A.M.
1 day ,, ,,		4 ,,
1 ,, ,, ,,		5 ,,
1 ,, ,, ,,		6 ,,
1 ,, ,, ,,		7 ,,

From this we may conclude that in lads of about 12 years old the morning rise usually begins between 3 A.M. and 7 A.M.

The chief part of the rise was completed by 9 A.M. After this hour the temperature usually remained at much the same height, until the evening fall began. Thus on

4 days the temperature remained much the same

from 9 A.M. to 5 P.M.=8 hours.

1 day	„	„	„	10	„	6	„	=8	„
1 „	„	„	„	10	„	5	„	=7	„
1 „	„	„	„	9	„	4	„	=7	„

On one day the temperature remained much the same from 8 A.M. to 1 P.M., then fell very slowly till 8 P.M.; afterwards the fall was much more rapid.

Hence it would appear that in boys of the age of 12 the temperature continues at about its maximum for 7 to 8 hours.

The Time at which the Maximum Depression was reached

varied greatly in these lads. Thus on

1 day it was reached at	7 P.M.
2 days " " 	9 "
1 day " " 	10 "
1 " " " 	11 "
1 " " " 	12 "
2 days " " 	1 A.M.

On six of these eight days the lowest temperature of the day was reached by 12 P.M. ; on two days this was not attained until 1 A.M. ; but the fall in the temperature after 12 P.M. on these two occasions was but slight, in each case amounting to only 0°·4 Fahr.

It thus appears that if in other persons of about the age of these lads our observations be continued till 12 P.M., we shall obtain the whole, or nearly the whole, of the daily variation of the body temperature.

The temperature does not begin to rise immediately after its minimum has been reached, but remains at about its lowest point during several hours before the morning rise begins ; thus on

2 days it remained at about its minimum	2 hours.
1 day " " "	4 "
1 " " " "	5 "
2 days " " "	8 "
1 day " " "	11 "

We thus see that in these observations the maximum depression is usually of shorter duration than the maximum elevation.

Thus we have learned that observations continued from 9 A.M. to 12 P.M. give us not merely the highest temperature of the day, but likewise the hour when the temperature begins to fall—the chief, and in many cases the whole, of the evening fall. With this information we are enabled to use some other though less complete observations, in which the temperature was not observed during the night after 12 P.M. We shall thus be able to confirm or to correct by a larger number of observations the foregoing conclusions.

On the Temperature of Healthy Persons of different Ages.

In this section we give the results of observations of persons of various ages in whom the temperature was taken only till 12 P.M. On two men, however, of about forty years of age, the observations were continued throughout the night and day ; and we are therefore able to compare the temperature of the whole twenty-four hours of persons of different ages.

The observations were made on the following persons :—

James Redfern, a child five years old, convalescent from rickets. His appetite was good. The ends of the bones were still enlarged, and there was some flattening and depression of the axillary regions of the chest.

Thomas Thompson and Alfred Rundell, aged respectively 11 and 13, were both in excellent health.

Frank Legg, 23 years old, convalescent from a very slight attack of rheumatic fever. He was free from pain, and his appetite was good.

Cornelius Farmelow, 40 years of age, and Alfred Purse, 55 years old, were both in good health.

Joseph Garnes, 48, had commencing locomotor ataxy. He was an unusually stout man with a capital appetite.

John Hilton, 68, suffered from slight rheumatic pains. His joints were slightly enlarged. His appetite was good.

Alfred Mountain we have already referred to.

We have, as on a previous occasion, thrown all the details of these observations into the form of a Table; the observations are given in detail at the end of this section and are deposited in the Archives.

Name.	Condition.	Date.	Time observation continued.	Max. temp.	Min. temp.	Daily variation.	Evening fall begun.
Redfern, æt. 5	Convalescent from Rickets	Dec. 15	9.25 A.M. to 12 P.M.	99.2	96.8	2.4	2 P.M.
		" 16	9.30 " to 12 "	98.8	97	1.8	2 "
		" 20	9.15 " to 12 "	99	97	2	3 "
Gibbs, æt. 11.....	Convalescent from Typhoid Fever	Dec. 7	9.30 " to 12 "	98.6	96.4	2.2	10 A.M.
		" 8	9.30 " to 12 "	99	97	2	7 P.M.
		" 9	9.30 " to 12.30 A.M.	99	97	2	7 "
Thompson, æt. 11...	Healthy	Dec. 8	9.30 " to 12 P.M.	99.6	97.6	2	7 "
		" 9	12 " to 12.30 A.M.	99.4	97.2	2.2	4 "
		" 10	9.30 " to 12.30 "	99.4	97.4	1.6	6 "
		" 12	9.30 " to 12 P.M.	99.2	97.2	2	7 "
Rundell, æt. 13.....	Healthy	Dec. 6	6 P.M. to 12 P.M.	99.2	97.2	2	8 "
		" 17	4 " to 1 A.M.	99.2	97.4	1.8	7 "
		" 18	4 " to 12 P.M.	98.8	97.2	1.6	7 "
Legg, æt. 23	Convalescent from Rheumatism	Dec. 10	9.30 A.M. to 12.30 A.M.	99	97	2	8.30 "
		" 11	9 " to 1 "	99.2	96.8	2.4	
		" 12	9 " to 12 P.M.	99.2	97.2	2	
		" 14	4 P.M. to 12 "	98.8	97.4	1.4	
Mountain, æt. 10 ...	Healthy	Dec. 13	11 A.M. to 12 "	98.2	...	1	9 "
		" 14	9 " to 12 "	99.2	...	2	6 "
		" 15	9.30 " to 12 "	99.2	...	1.6	6 "
		" 16	9.20 " to 12 "	99	...	1.6	7 "
		" 17	9 " to 12 "	99.2	...	1.8	7 "
		" 28	2.45 P.M. to 11 "	99	...	1.2	7 "
		" 29	9.15 A.M. to 12.15 A.M.	99.2	...	2.2	6 "
Farmelow, æt. 40 ...	Healthy	Dec. 7	24 hours	98.6	97.2	1.4	9.30 A.M.
		" 8	"	98.6	97.2	1.4	9.30 "
		" 9	"	98.6	97.4	1.2	5 P.M.
		" 10	"	98.4	97.6	0.8	3 A.M.
		" 11	"	99	98.2	0.8	
		" 19	"	99	98.4	0.6	
Garnes, æt. 48	Slight locomotor ataxy	Dec. 7	"	99.2	98.2	1.0	
		" 5	"	99	...	0	
		" 3	"	99	98.9	1.0	
		" 4	"	99.4	98.4	1.0	
Purse, æt. 55.....	Healthy	Dec. 7	9.30 A.M. to 12 P.M.	98.4	97.6	0.8	
Hilton, æt. 68	Chronic Rheumatism	Dec. 7	9.30 " to 12 "	98.6	98	0.6	

We next extract from this Table the average maximum temperature and the average daily variation at different ages.

5 years of age. Redfern. 3 observations.

Average maximum temperature	99° Fahr.
Average diurnal variation	2°·06 Fahr.
Evening fall begun between.....	2 P.M. and 3 P.M.

10 and 11 years. Mountain, Gibbs, and Thompson. 14 observations.

Average daily maximum temperature	99°
Average daily variation	1°·8
Evening fall begun between	4 P.M. and 7 P.M.

It begun once at 10 A.M. and once at 9 P.M.

23 years. Legg. 3 observations.

Average daily maximum temperature.....	99°·1
Average daily variation	2°·1
Evening fall begun	6 P.M. and 8 P.M.

Average of all the foregoing observations, which were all made on persons under 25 years of age :—

Average maximum daily temperature.....	99°
Average daily variation	1°·9
Evening fall begins usually between 2 and 8 P.M.	

These general conclusions are almost identical with those afforded by the more complete observations made on Mountain and Rundell, and we think they may be accepted as generally true of all persons under 25 years of age.

We now give the averages of the persons over 40 years of age :—

40 years. Farmelow. 6 series of observations, which were continued through the day and the night.

Average maximum daily temperature.....	98°·7
Average diurnal variation	1°·0

48 years. Garnes. 5 series of observations, each continued for 24 hours.

Average maximum daily temperature	99°
Average diurnal variation	0°·76

55 years. Purse. One observation.

Maximum temperature	98°·4
Daily variation	0°·8

68 years. Hilton.

Maximum temperature	98°·6
Daily variation	0°·6

Averages of all the persons over 40 years of age :—

Average maximum daily temperature	98°·8 Fahr.
Average daily variation	0°·87 „

We are now in a position to compare the temperature of persons under 25 with that of persons over 40 years of age.

Average daily maximum temperature of all the observations	
made on persons under 25 years	99° Fahr.
Average daily variation of the temperature of the same	
persons	1°·9
Average maximum temperature of persons over 40	98°·8
Average daily variation	0°·87

From this Table it appears that the daily variations in old people is considerably less than that of young people; in fact the variations in persons over 40 is only half that of persons under 25 years.

On the other hand, the daily maximum temperature is much the same both under 25 and over 40.

But the difference is not merely in the amount of depression, but in the manner of its occurrence. In young people we get in the evening a very rapid fall, and the minimum temperature of the day is quickly reached; often, indeed, in three or four hours. In persons over 40, whose temperature was taken through the day and night, so rapid a fall rarely occurs; but the temperature usually declines very slowly, and as soon as the minimum is reached it again begins to rise, so that not only is the amount of the evening fall less in these older persons, but the period of the depression is also shorter, generally very much shorter.

It may here be noted that on some days, even when the temperature was observed for twenty-four hours, no diurnal variation occurred in persons over 40 years of age. But the temperature of these older differs in yet another respect from that of younger persons; thus apparently the diurnal fall does not observe any particular time, but occurs sometimes in the middle of the night, and at other times in the morning at about 9 A.M.

PART II.

Concerning the influence of Food on the Temperature of Healthy People.

In a previous section a considerable diurnal variation in the temperature, often amounting to two degrees, has been shown to occur.

It is important to ascertain whether this variation is produced by food or is due to other causes. Our present section is devoted to the solution of these questions.

We shall at first turn our attention to the observations made on the lads Rundell and Mountain. As these were continued night and day, without any interruption, and as we have accurate accounts of the quantity and the nature of their food, it is obvious we shall obtain much more trustworthy conclusions from these than from less elaborate and exact observations.

These two lads were about twelve years of age. The observations

from which we now draw our conclusions will be found in full at the end of the sections treating of the temperature of health, and on the influence of baths on the heat of the body.

We hope to show the high probability that the diurnal variation of the temperature is altogether independent of food; and, while attempting to establish this, we shall speak first of the influence of breakfast, secondly of the tea, and lastly of the dinner.

Concerning the behaviour of the temperature before and after breakfast, it may be stated that these boys took breakfast at 6 A.M., dinner at 12, and tea at 5 P.M.—no food being allowed at other times, with one exception, which at the proper place will be noted and referred to.

Is the daily rise of the body temperature due to food? During the early morning hours, before breakfast, the temperature rose considerably; indeed rather more than half the diurnal rise took place before 6 A.M., the breakfast time of these lads, showing that some of this rise is not due to food. This part of the rise, it must be apparent, could not be produced by food, unless, indeed, it be attributed to the tea of the previous evening, a supposition impossible to maintain, as ten hours elapsed between the tea and the beginning of the morning rise. The chief influence of a meal on the body is expended during the third to the fifth hour, and then gradually declines and usually ceases altogether in ten hours, a fact shown by the variations in the urea of the urine after a meal. During the three first hours the quantity of urea gradually increases, then for an hour or more the maximum quantity is maintained, after which it gradually grows less, till the standard of inanition is reached.

Now in all our observations during the early hours of the evening, when the influence of the evening meal was greatest, the temperature fell considerably, and the rise of temperature did not begin till the effects of food must have entirely ceased.

We are thus driven to admit that half the daily rise is due to other causes than food.

The annexed Table gives a summary of the observations elsewhere recorded in detail, and includes the whole of the morning rise, which was always accomplished by 9 A.M.

The first column gives the name of the lad; the second the hours before breakfast during which the temperature rose; the third the rise before breakfast; the fourth the hourly rise; the fifth the hours of observation after breakfast; the sixth the rise during this time; the seventh the hourly rise after breakfast; and the last column gives the food taken during the investigation.

Name.	Temperature taken from	Temp. rose.	Rose per hour.	Temperature taken from	Rise.	Rise per hour.	Breakfast.
Mountain	3 A.M. to 6 A.M.	° F. 1.0	0.33	6 A.M. to 9 A.M.	° F. 0.6	0.2	Tea with little milk in it.
	3 " " 6 "	1.0	0.33	Ditto.	0.6	0.2	
	2 " " 6 "	1.2	0.3	"	0.4	0.13	Breakfast-cup of cocoa, & $\frac{1}{2}$ round of bread & butter.
	2 " " 6 "	1.0	0.25	6 " " 8 "	0.8	0.4	Cup of cocoa.
	3 " " 6 "	2.0	0.66	6 " " 9 "	0.6	0.2	"
	1 " " 6 "	1.2	0.24	Ditto.	0.6	0.2	"
	3 " " 6 "	0.8	0.26	"	1	0.33	"
	2 " " 6 "	1.4	0.35	"	0.6	0.2	"
	4 " " 6 "	0.8	0.4	"	1.6	0.53	$\frac{1}{2}$ pint of milk, $\frac{1}{2}$ round of bread.
	2 " " 6 "	1.0	0.25	"	1	0.33	Cup of cocoa.
	4 " " 6 "	0.4	0.2	"	1.0	0.33	"
	3 " " 6 "	1.2	0.4	"	0.4	0.13	"
	2 " " 6 "	1.2	0.3	"	0.8	0.26	$\frac{1}{2}$ pint of milk, $\frac{1}{2}$ round of bread and butter.
	Average.....		0.328	Average.....		0.264	
Rundell...	2 " " 6 "	1.2	0.3	"	0.8	0.26	

To what extent was the elevation following breakfast due to that meal? Probably to a very small extent; for:—

1st. The rise after breakfast was somewhat less than the rise before it, the Table showing that the average hourly rise of all the observations before breakfast was $0^{\circ}328$ Fahr., while the hourly average rise after this meal was $0^{\circ}264$ Fahr. It thus appears that, apart from food, the causes which influence the diurnal variation are adequate to explain the rise which happened after breakfast.

2nd. The rise after breakfast if due to food should be in proportion to the quantity taken; but no such relation occurred. The rise, as the Table shows, was somewhat greater after a cupful of very weak tepid tea than after a fairly hearty meal.

3rd. On the morning when these boys took only a cupful of tea, they may be considered to have practically gone without breakfast; yet on these days the rise took place as usual, showing that the greater part of the after breakfast rise, and in all likelihood the rise on other days, must be independent of food.

Still restricting our attention to the observations on Mountain and Rundell, we pass on to consider how far the evening fall in the temperature is affected by the evening meal.

These boys took tea at 5 P.M., always a very hearty meal, often the largest of the day, and generally consisting of two, often of three eggs, bread and butter, with tea or cocoa. They had no supper, and were allowed to fall asleep at their pleasure, and were not awakened when the temperature was read off. Due care was taken that they were well covered with bed-clothes.

In sixteen observations the temperature after tea fell immediately and

continuously, until it reached the lowest point of the night. In many cases the evening fall had begun before the tea; in one case only did it rise after the meal, and on this occasion to the extent only of $0^{\circ}2$ Fahr., and for a very short time.

On these occasions, as the fall occurred immediately after, and notwithstanding a hearty meal, and moreover as the boys were in all respects placed in the same conditions throughout the day, it is obvious that we must admit that there are certain circumstances irrespective of food which determine the diurnal variation of the temperature. Is all this fall due to these unknown circumstances? Or must we admit that a portion of the previous rise is due to the food, and as its heat-producing effects wear off, and as the inanition period is reached, a fall takes place equal in amount to the previous rise determined by the food?

We will now give reasons which lead us to conclude that the total of the fall is due to circumstances wholly apart from the food.

The question to decide is, how much of the evening fall is to be accounted for by those circumstances (irrespective of food) that determine the diurnal variation, and how much, if any, is due to the withdrawal of the influence of food on the body. It must be evident that the fall which occurred while the influence of the food was at its highest must be wholly attributed to other circumstances. We need hardly dwell on this point; for if the fall is due to the diminished or exhausted influence of the food, such a decline could not occur when the meal was exerting its greatest effects; therefore that part only of the fall which took place when the effects of the meal had begun to diminish or had ceased can be attributed to the withdrawal of the influence of food. But in all cases the principal part of the evening fall occurred while the influence of the tea must have been at its height, and in many instances the whole of this fall had taken place at this time—the chief part of this evening fall having on all occasions occurred before 11 P.M., and was, indeed, very often by this time at the lowest point. Thus in those cases only where the fall continued after 11 P.M., a very small portion, if any, of this fall could be due to the declining influence of food.

In this Table we give, in the first column the date, in the second the amount of fall after 10 or 11 P.M., and in the third the hour of the night when observations were discontinued.

On the following days the boy took no bath:—

Date.	Amount of fall.	Observation discontinued
Dec. 13	No fall after 10 P.M.	at 12 P.M.
„ 14	„ 11 „	„
„ 15	„ 10.30 „	„
„ 16	A fall of $0^{\circ}4$ after 10 „	„
„ 29	No fall after 10 „	12.15
Jan. 2	„ 10.30 „	through the night.
„ 6	A fall of $0^{\circ}8$ after 11 „	„

Date.	Amount of fall.	Observation discontinued
Jan. 12	A fall of $0^{\circ}4$ after 10 P.M. . . .	through the night.
„ 13	„ $0^{\circ}2$ „ „ „	„
„ 14	„ $0^{\circ}8$ „ „ „	„
On the following days a bath was given to the boy in the morning.		
Dec. 18	A fall of $0^{\circ}6$ after 10 P.M. . .	at 12 P.M.
„ 20	„ $0^{\circ}2$ „ „ „	„
„ 21	No fall after 10 „	„
Jan. 1	„ „ 11 „	through the night.
„ 6	A fall of $0^{\circ}2$ after 10 „	„
„ 8	„ „ „ „ „	„
„ 9	„ „ „ „ „	„
„ 10	„ $0^{\circ}4$ „ „ „	„
„ 11	„ $0^{\circ}2$ „ 11 „	„

Summary of this Table.

Observations recorded on ten days when no bath was taken :—

In 5 of these no fall after 10.

„ 1	a fall of $0^{\circ}2$	„ „
„ 2	„ $0^{\circ}4$	„ „
„ 2	„ $0^{\circ}8$	„ „

Observations recorded on 9 days when baths were taken in the morning :—

In 2 there was no fall after 10 to 11 P.M.

„ 4	a fall of $0^{\circ}2$ occurred	„ „ „
„ 1	„ $0^{\circ}4$	„ „ „
„ 1	„ $0^{\circ}6$	„ „ „
„ 1	„ $1^{\circ}0$	„ „ „

These two Tables may, we think, be fairly thrown together, for we cannot understand how baths given in the morning should interfere with the evening temperature. Thus we have 19 series of observations ; and in 7 of these no fall occurred after the chief influence of the meal had ceased.

In 5 cases a fall of $0^{\circ}2$ occurred ; but we think a variation so slight may be disregarded, as it might, and probably was often, caused by some accidental circumstance, as the movement of the body in bed or some similar cause—an assumption strengthened by the fact that this slight decline was often noted only once, and at the time of the next observation the temperature had recovered itself.

These observations, therefore, may be thrown together, giving the result that in 12 of the 19 observations the food appears to have had no influence on the evening fall. Of the remaining 7 observations, after the supposed influence of the food had passed away,—

In 3 there was a fall of $0^{\circ}4$

„ 1	„ „	$0^{\circ}6$
„ 2	„ „	$0^{\circ}8$
„ 1	„ „	$1^{\circ}0$

It appears, then, that the fact of the fall being in the majority of cases independent of the food, is presumptive evidence that the fall which occurred on some occasions after 11 must be due to other causes than the withdrawal of the influence of food.

The Influence of Dinner on the Temperature.

Observations made on the temperature before and after dinner furnish * further illustration of the non-influence of food on the temperature of the body. If food can raise the temperature, we should certainly expect this to occur after dinner, especially in Mountain's case, if we bear in mind that his breakfast was so small, that its effects on the body must have ceased altogether before 12, his dinner hour ; and hence the influence which food can be supposed to exert on the temperature would in his case be manifest after dinner.

The appended Tables give the results of the observations made on Mountain and Rundell. We have not restricted ourselves to those days when the temperature was continuously taken through both night and day, this limitation being evidently unnecessary, but we have used all the observations made on these lads. In every case their breakfast was taken at 6 A.M., and their dinner at 12, or shortly after this.

Name and Date.	Time before dinner.	Rise or Fall.	Hourly.	Dinner	Time after dinner.	Rise or Fall.	Quantity of food taken at dinner.
Mountain.							
Dec. 14	9 to 12	Rise 0.6	0.2	12	12 to 3	Rise 0.2	Full dinner.
					3 „ 5	Fall 0.4	
„ 15	10 „ 12	„ 0.6	0.3	12	12 „ 3	Rise 0.2	„
					3 „ 5	Fall 0.2	
„ 16	9 „ 12	„ 0	0	12	12 „ 3	Fall 0.2	„
					3 „ 5	Rise 0.4	
„ 29	9 „ 12	„ 0.4	0.13	12	12 „ 3	Rise 0.4	„
					3 „ 6	Fall 0.8	
„ 30	9 „ 3	„ 0.4	0.06	3	3 „ 5	0.0	Dinner moderate.
Jan. 2	9 „ 12	„ 0	0	12	12 „ 3	Rise 0.6	„
					3 „ 4	Fall 0.4	
„ 6	9 „ 12	Fall 0.6	0.2	12	12 „ 1	Rise 0.4	Full dinner.
					1 „ 5	Fall 0.4	
„ 12	9 „ 12	„ 0.2	0.06	12	12 „ 3	Rise 0.2	„
					3 „ 5	0.0	
„ 13	9 „ 12	At first a rise of 0.2 & then a fall of 0.4	0.06	12	12 „ 3	0.0	Slight dinner.
					3 „ 5	0.0	
„ 14	10 „ 12	0	0.0	...	12 „ 3	Fall 0.2	Full dinner.
					3 „ 5	Rise 0.6	
Rundell.							
Jan. 6	10 „ 1	0	0.0	1	1 „ 4	Rise 0.2	„
					4 „ 6	Fall 0.2	

* The detailed observations will be found in the Charts which give the diurnal variation of the temperature and the influence of bath (Royal Society's Archives).

This Table shows the results of eleven observations; and we gather that the rise between 9 A.M. and 12 (noon) was always very small; and on some days none took place, as the hourly rise during these 3 hours on

4 occasions was		<i>nil</i>
1 occasion it was		0°·2
1 „ „		0°·3
1 „ „		0°·13
2 occasions it was		0°·06

In two instances there was an hourly fall, once of 0°·2 and once of 0°·6.

We now add a Table indicating the alterations in the temperature during three hours after dinner.

On 4 days the temperature rose		0°·2
„ 2 „ it fell		0°·2
„ 2 „ it rose		0°·4
„ 1 day it rose		0°·6
On two days there was no alteration.		

So slight a rise of 0°·2 is so easily produced by accidental causes, that, as we have before said, it may be almost disregarded. On this supposition, then, it appears that on six of the ten days the rise was *nil* or practically unappreciable, and on other days the rise was very small.

It may be fairly said that we shall elicit surer information as to the influence of the dinner, if we observe how the temperature comported itself between three and five o'clock, when the food influence on the body may be supposed to be at the maximum. The following Table exhibits the temperature during these hours, in the case of Mountain :—

On 2 days the temperature remained unaltered.	
„ 2 „ it fell	 0°·2
„ 3 „ „	 0°·4
„ 1 day „	 0°·8

The temperature rose on two days only, and on each instance 0°·4.

Here we close our investigations on the influence of food on the lads Mountain and Rundell. We cannot absolutely say that food does not in any case raise the body temperature; yet it is clear that its influence in this respect, if any, on persons in health and well nourished is very slight indeed.

We may further add that these observations are opposed to the statement made by Dr. John Davy, to the effect that a fall in the temperature occurs immediately after food.

We give a few further tabular observations on the after-dinner temperature made on Redfern, Gibbs, Thompson, Farmelow, and Garnes.

Temperature of the Human Body in Health.

Name.	Date.	Dinner hour.	Rise in temperature after dinner.
Redfern	Dec. 15	12	0°0
	" 21	"	0°4
Gibbs	" 7	"	Constant fall.
	" 9	"	0°0
Thompson.....	" 8	"	0°0
Farmelow	" 9	"	0°6
	" 10	"	0°0
	" 11	"	0°4
	" 19	"	0°2
Garnes	" 5	"	0°0
	" 6	"	0°0
	" 7	"	0°6
			Average rise 0°·18

Thus in seven of these twelve observations no appreciable rise took place.

In five the temperature rose, the average rise being 0°·4. Breakfast was taken at 6 A.M., and no further food allowed afterwards until 12. It may be objected, in respect of these observations, that the influence of the breakfast had not passed away by dinner time, and that the temperature elevated by this meal was maintained by the dinner. As the influence of the breakfast may not have passed off by dinner time these observations are not so trustworthy in the settlement of this question of the influence of food on the temperature as those made on Mountain. We give them, however, for what they are worth, believing they serve in some degree to corroborate our previous conclusions.

It is, however, right to refer to some observations in which a very considerable rise occurred after a late breakfast.

These were made on three persons in ill-health. One man, 35 years of age, suffered from hemiplegia; another, 32 years, with hemiplegia and dilated heart; and the third, 21 years old, was the victim of some obscure disease. His spleen was very much enlarged, and he occasionally passed large quantities of blood with his urine. These patients abstained from food from tea (5 P.M.) one day till breakfast on the following day, taken either at 10 A.M. or a little later.

These observations, for the sake of clearness, are thrown into a Table. The first column shows the time before breakfast the temperature was taken; the second gives the temperature of the body at the time of commencing each observation; the third shows the amount of the rise before breakfast; the fourth gives the rise after breakfast; and the fifth column shows the duration of the rise.

Time before breakfast.	Temperature.	Rise before food.	Rise after food.	Duration of the Rise.	
h m	°	°	°	h m	
1 15	96·6	0	1·2	45	Remained fixed.
50	97·4	0·4	1·0	40	Remained the same.
1 5	98	0	0·6	1 15	"
45	97	0	1·4	50	Then fell 0°·4.
3 15	97·6	0	0·4	4 15	
1 5	97·6	0	1·0	1 25	
45	97·6	0	0·2	45	
1 10	96·6	0	0·8	1 5	
3 15	...	0·4	0·8	2 15	
Average	...	0·09	0·82	1 28	
45	98	0·2	0·8	18	Mary Lyon.

It thus appears that after breakfast the temperature of these men rose considerably, the average being $0^{\circ}\cdot 8$, sufficient, it may be said, to show that the food is capable of causing an elevation in the temperature of the body, especially as in many of the days no rise took place before breakfast, the temperature having been taken at this time for several hours.

We are constrained to admit that perhaps this rise in the axilla was due to the food ; although opposed to this admission, we might urge the fact that on three days, when the temperature of Jones and Tarves was taken during the morning hours, while they were kept fasting, an average rise of $0^{\circ}\cdot 7$ occurred, being almost identical with that which took place on other days when they partook of food.

Assuming that this rise in the axilla was really due to food, How was the rise caused ? Was it due to a general elevation of the body temperature, owing to increased consumption of the food ? or was it due to other causes ? It could hardly be due to increased oxidation of food, for we should expect the elevation to be most marked at the time during which the food was most rapidly absorbed and carried to the tissues. But in these men the rise in the temperature occurred much sooner than this, being completed on an average in an hour and twenty-eight minutes, and in several cases in fifty minutes, in some even in thirty, although there was a considerable rise on these days ; yet at the time the influence of food would be expected to be most marked the temperature either remained unchanged or in some instances it even fell.

Further, it may be remarked that were the rise after breakfast due to combustion of the food, we should expect that a similar rise would occur after the dinner, which was a heartier meal than the breakfast ; but the rise after dinner was much less than that after breakfast.

TARVES.

Nov. 13.	Dinner at 1.	No rise.	Observations continued till 5 P.M.
„ 15.	„ 4.20.	Rise 0°·6	„ 8 „

JONES.

Nov. 9.	„ 4.10.	„ 0°·6	„ 8 „
„ 10.	„ 1.15.	„ 0°·4	„ 5 „
„ 11.	„ 1.10.	„ 0°·8	„ 5 „
„ 14.	„ 12.15.	„ 0°·4	„ 6 „
„ 13.	„ 1.30.	„ 0°·4	„ 5 „

PERRIN.	„ 4.10.	No rise.	„ 8 „
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MARY LYON.	„ 1.30.	Rise 0°·2	„ 5 „
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Average rise 0°·37

It may, however, be fairly objected to this argument, that the influence of the breakfast on the body had not ceased before that of the dinner begun, and that the dinner prevented the possible fall after the breakfast if dinner had not been taken.

Thus, to summarize very generally the conclusions we have arrived at:—There is a diurnal cycle in the temperature of the body, much more evident in young than in middle-aged or old people; in elderly people, indeed, the daily variation is often very slight, and sometimes altogether absent; further, this diurnal variation is due to other causes than food, which if operative in any degree in producing elevation of the temperature, is so, if at all, to a very small extent.

PART III.

On the Influence of Cold Baths on the Temperature of the Body.

We undertook these experiments from a wish to learn the influence of the cold bath on the temperature of the surface and internal parts of the body, and to ascertain if it were possible, in any degree, to cool the whole body; and if so, to what extent the temperature could be lowered, and how long this depression would continue.

Our observations were made in the winter months. The temperature of the person fixed upon for experiment was first carefully ascertained either in the axilla, the rectum, or under the tongue. He was then immersed in a bath of a temperature of 60° Fahr. for a time varying from 1 to 35 minutes in the several series of experiments. The body was covered by the water up to the chin. Immediately on the return to bed the temperature was again ascertained, and every few minutes afterwards. In some instances we took the temperature under the tongue during the immersion; but these notes we fear are not quite correct, although we spared no pains, for the patient's teeth chattered so much as to prevent the steady closure of the lips.

We shall now give a tabular extract of the effects of the cold bath, first on the heat of the surface, and afterwards on that of the internal parts.

Name.	Time of bath.	Temp. fell in axilla to	Mainly recovered in	Entirely recovered in	Temp. fell in mouth or rectum.	Recovered in
	mins.	°	mins.	mins.		
Redfern, æt. 5	1	95·5	25	50		
	1	95	13	48		
	5	93·4	67	77		
	5	93	48 ?	80		
	5	92	58	123		
	5	92	75	120		
	5	92	70	75		
	15	90	88	98		
	30	87	105	125		
	35	89	135	135		
Gibbs, æt. 11.....	1	96	45			
	1	97	48			mins.
Thompson, æt. 11...	1	97	33	60	0	0
	5	95	20	100	0·6	100
Mountain	10	94·6	50	50	1·8	
Legg, æt. 23	10	96	22			
Mountain, æt. 10 ...	16	...	...	...	1·2	69
	30	...	...	...	2·8	43
	1	...	...	...	0·8	70
	5	...	...	...	0	
	15	...	...	...	1·1	
Walker, æt. 48	15	92	...	280	1·1	280
Purse, æt. 55.....	5	93·6	...	...	2·2	2 hours 17
Hilton, æt. 68	5	95·3	37			mins.&more

This Table exemplifies, as was to be expected, that the cold baths considerably cooled the surface of the body, and that the longer the immersion the greater was the depression of the temperature of the skin. Thus this Table shows that on some occasions the temperature of the axilla fell to 87° Fahr.; but a depression so great occurred only when the bath was continued for a considerable time, for a period, indeed, varying from 15 to 35 minutes; and even this amount of depression was of short duration. To illustrate this effect we give three extracts from the preceding Table. A bath of 60° Fahr. for one minute reduced the temperature of a child five years old to 95° Fahr., but in 13 to 25 minutes the temperature of the axilla had nearly recovered itself. With a bath of the same temperature continued five minutes we reduced the temperature to 92°; but in 48 to 75 minutes after leaving the bath the axillary temperature had nearly recovered. Nay, even after a bath of 35 minutes the temperature only fell to 89°, and recovered itself in 135 minutes. The greater part of the lost heat was very quickly restored, and then the axilla more slowly regained the rest of the lost temperature.

Influence of Cold Baths on the Temperature of internal parts of the Body.

Cold baths reduce the temperature of internal parts of the body, but

the reduction is considerably less than that of the surface. Thus we lowered the temperature under the tongue or in the rectum from 0°·6 to 2°·8 Fahr., the amount of depression being, of course, proportional to the duration of the bath.

The duration of the depression varied greatly in different persons. Thus on some occasions the lost heat was restored in an hour ; in others not for several hours, three, four, or more ; but very soon after leaving the bath the greater part of the lost heat was restored, the remaining slight depression passing off much more slowly. Our observations elicited the rather curious fact that the time the body takes to recover its temperature holds no relation to the amount of depression ; thus in some instances, when with great depression, the recovery was speedy, while on other occasions, with but slightly depressed temperature, the recovery was slowly effected.

We noticed, too, that many times the internal parts did not become cooled under the actual operation of the bath, but the temperature of the internal parts fell gradually for some time after the bath. The explanation we would offer of this curious fact is, that during the bath much heat is withdrawn from the surface, and the cold contracting the blood-vessels lessens greatly the quantity of blood passing through the skin. Heat is thus not abstracted from deep parts by cooling of the blood, but simply by conduction. On quitting the bath, the blood-vessels of the skin become widely dilated, and the blood then passing quickly through the cold skin becomes cooled, and reduces the temperature of deep parts.

Influence of the Cold Bath on the Temperature of the Body after the discontinuance of the Bath.

We first give the hour when the evening fall begun on the bath days :—

Redfern	12 to 4 P.M.
Gibbs	3 P.M.
Thompson	4 to 6 P.M.
Mountain	6 P.M.

On comparing this Table with the one given in the section treating of the temperature in health, it will be found that the time when the temperature begun to fall is much the same whether a bath be given or not.

For the sake of comparison we put side by side the hour the evening fall begun on bath and non-bath days.

Name.	No bath.	Bath.
Redfern.....	2 to 3	2 to 4
Thompson and Mountain	4 to 7	4 to 6*.

* It hitherto escaped our notice that the younger the person the sooner in the day does the evening fall begin. Thus in Redfern it began between 2 and 3, in Thompson and Mountain between 4 and 7, and in Purse and Hilton between 9 and 11.

Amount of evening fall on bath days :—

Name.	Amount of fall.	Obs. continued till
Redfern	2.2	12
Thompson and Mountain..	2.1	12

We extract from a previous section the amount of the evening fall on non-bath days :—

Redfern	2.06	12
Mountain	2.2	whole night
	1.8	12

These Tables show that the bath exerts no influence on the evening fall.

Table of the hour when the minimum temperature of the day is reached on bath and non-bath days, showing that, in this respect, cold baths have little or no influence :—

Bath days.

Redfern	between 5 and 8.
Mountain and Thompson..	between 10 and 12.

Non-bath days.

Redfern	6.30 to 8.
Mountain and Thompson..	9 to 12.

PART IV.

Influence of Hot-water and Vapour Baths on the Temperature of the Body.

We next turn our attention to the influence of hot-water and vapour baths on the temperature of the body; and we shall first attempt to ascertain the influence of hot baths on the temperature of the body, both at the time of immersion and during the rest of the day. We have, as usual, extracted and tabulated the chief data from the charts appended to the end of this section. The temperature was obtained by placing the thermometer under the tongue while the person was in the bath. The method of taking the temperature is always noted in the charts.

Name.	Date.	Temp. of bath.	Time in bath.	Rise of temp. of the body.	Evening fall of temp. begun.	Amount of evening fall.	Observations continued to	Min. temp. reached
			mins.	° F.	P.M.	°	P.M.	P.M.
Mountain, æt. 10 ...	Dec. 21	106	20	3.4	12	1.8	12	10
	Jan. 1	105 to 108	24	4.6	...	2.0	All night.	11
	" 3	97 to 101	134	1.8	5 & 8	2.6	"	11
	" 4	99 to 103	40	2.6	8	2.2	"	11
	" 5	99 to 101	45	1.8	6	2.2	"	12
Thompson	Dec. 6	100 to 103	20	1.0	5	2.0	P.M. 12	11
Rundell	" 20	105	25	1.6	6	1.4	12	9
	" 21	106 & 107	15	2.8	7	1.4	12	10
Ryman, æt. 25	" 19	105	20	3.4	9	2.2	12	11
	" 20	105	20	4.6	...	1.6	12	
	" 21	Hot	20	1.8	...	1.2	12	
	" 22	105	20	2.8	...	1.8	12	
Tarves, æt. 32	...	107 to 109	40	4.6				
Luff, æt. 16	Jan. 22	106	87	3.6				

From this Table we learn that in all cases the temperature of the body rose in the hot bath, this elevation, as might be expected, varying with the temperature and duration of the bath. It varied from 1° Fahr. to $4^{\circ}6$ Fahr.; or, to put it in another and more striking way, we raised the body temperature to 103° and 104° Fahr., a severe fever height. Is it possible to bring the temperature of the body to that of the bath? As it is impossible to remain in a very hot bath sufficiently long to enable us to determine this question, we must examine those experiments in which the temperature of the bath was not very high. We were compelled in a short time to discontinue the experiment with a very hot bath on account of the great weakness induced by it. Yet as the temperature continued to rise so long as the patient remained in the hot water, it is probable that, if adequate time could have been allowed, the temperature of the body would have become identical with that of the bath.

The charts show that a bath of moderate temperature, as 101° to 102° , will raise the body temperature to that of the bath. Whilst making several of these series of observations the bath temperature was recorded simultaneously with the temperature of the body, and the figures are given in the charts, as with Mountain on Jan. 3rd, 4th, and 5th, and with Mooney and Luff on Jan. 22nd. Thus it is clear that the temperature of the body may be raised to that of a bath at $101^{\circ}8$.

Influence of Hot-water Bath on the Temperature of the Body during the rest of the day after the Bath.

The evening fall begun in Mountain, Thompson, and Rundell between 5 P.M. and 8 P.M.

The average diurnal variation of all the observations
in the above-named lads, all about the same age, was . . $1^{\circ}9$ Fahr.
Of Mountain alone $2^{\circ}1$ „

The minimum temperature of the day of these three lads was reached between 9 and 11 P.M., the average time being 10.

If these results are compared with those obtained from the observations made on the same lads on the bathless days, it will be seen that the two sets of figures entirely agree; that, in fact, hot-water baths, except at the time of immersion, exert no influence on the body temperature.

On the Influence of Hot-vapour Baths on the Temperature of the Body.

The temperature of the body is always raised by the hot-vapour bath, the amount of elevation, as might be expected, being proportionate to the heat and duration of the bath, as shown in the following Table:—

Breathed the steam of the bath.

Name.	Temp. of body before bath.	Raised during bath to	Amount of elevation.	In mins.	Temp. of bath.
Mooney . .	98°	101·4	3°	25	103°
„	..	100·2	..	..	101°?
„	98·8	96·6	0·8	33	100°
„	98·4	100	1·6	64	97° and 98°
Church . .	98·8	100·4	1·6	28	90° to 94°

Breathed air of outer room.

Luff	..	101	..	..	103° to 105°
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In some of the observations we have stated only the time occupied in effecting the rise, as on these days the bath, before it was entered, was first heated to the temperature at which it was maintained; while on the other days the bath was entered immediately the steam was turned on, being thus occupied while the temperature of the room was rising.

These experiments enable us to learn the rapidity with which the body may lose heat; for as the body of the person experimented upon was heated considerably higher than could be maintained by physiological processes, so this unnatural elevation is speedily lost by evaporation, radiation, and conduction. As the loss of heat sustained varied with the temperature to which the body was raised, we shall speak first of the cooling of the body from a high temperature, and next from a temperature a little above that of health. It was found that heat was much more quickly lost under the first than under the latter conditions.

We now give a Table to show the rapid loss of heat when the temperature of the body has been raised considerably, for instance to 102° and 104° Fahr. :—

Name.	Date.	Fall. ° F.	in
Mountain	Dec. 21	2·2	10 minutes.
Rundell	Dec. 21	1·8	10 „
Ryman	Dec. 18	3·0	13 „
„	Dec. 22	2·2	8 „
Mooney	Jan. 18	1·4	10 „

A degree of heat was thus lost in 4·7 minutes. As an interval of five minutes sometimes elapsed between the testings, we can hardly speak with the exactness indicated by the figures. It is better to say the body may lose a degree of heat in less than five minutes.

The following Table shows that the loss of body heat is much less rapid when the body is less heated, one degree being lost in 40 minutes :—

After hot-water bath.				
Name.	Date.	Fall from	of	in
	Jan. 18	100	0.6	37 minutes.
Mountain ..	Dec. 21	100	0.6	13 „
„ ..	Jan. 1	100	0.6	20 „
Rundell	Dec. 21	100	0.8	20 „
Thompson ..	Dec. 6	100	0.6	25 „
Ryman	Dec. 21	100.2	1.0	57 „

After hot-vapour bath.				
Mooney		99.4	0.6	33 minutes.
„		100	0.6	36 „
„		100.4	1.2	42 „
Luff.....		100	0.6	15 „
Church		100.4	0.6	20 „

Can the figures last given be accepted as about the usual rate at which heat is lost by the body in health?

We shall now try to ascertain the source of this increase of body heat under a warm-water or hot-vapour bath.

Our experiments with vapour-baths afford the more complete solution ; and the following remarks will be limited to them, though it is evident that they will also hold good in the case of hot-water baths.

This increase in the heat of the body may be due to

1. Accumulation of heat in the body.
2. Absorption of heat from the bath.
3. Both of these circumstances.

Some of the increased heat was undoubtedly due to an accumulation of heat in the body.

It is evident that a person in a hot-vapour bath of the temperature of the body, and when breathing the steam, could lose no heat by evaporation or radiation or conduction, the only means of withdrawing heat from the body. If the production of heat is not diminished *pari passu* with its loss from the body, then heat will accumulate, and the temperature of the body will be raised.

Two observations show this to be the case. Thus with Mooney on Jan. 29th and Church on Jan. 22nd the temperature of each respectively was raised to 100° and 100°.4, while the bath was never more than the temperature of their bodies. We show this in a Table :—

Name.	Temp. of body before bath.	While in bath.	Rise.	Temp. of bath.
Mooney ..	98.4	35 mins	100 = 1.6	97° and 98°
Church ..	98.8	24 „	100.2 = 1.4	highest 94

Here it was impossible that the heat which raised the temperature of the body could be obtained from the bath, itself never hotter than the bodies of the boys before undergoing the experiment. If the formation of heat was lessened so as exactly to meet the diminished loss by conduction and radiation, the heat of the body would have continued at the same point; but this was not the case, and thus it appears that the formation of heat cannot be suddenly lessened to such an amount.

Thus the increased heat of the body ensuing from a vapour-bath is certainly in part due to accumulation of heat, which under other circumstances is lost by evaporation and radiation. Is all the heat imparted to the body by the vapour-bath to be accounted for in this way? Some part must, in the nature of things, be absorbed from the bath, and is evidenced in our experiments, the elevation being too rapid to be caused solely by an accumulation of heat in the body.

ON THE EFFECTS OF SULPHATE OF ATROPIA ON THE NERVOUS SYSTEM OF FROGS. By SYDNEY RINGER, M.D., *Professor of Therapeutics at University College*, and WILLIAM MURRELL, L.R.C.P., *Sharpey Physiological Scholar*.

IN the course of an experimental investigation made with the view of elucidating the true nature of tetanus, we had occasion to repeat many of Dr T. R. Fraser's well-known experiments on the influence of atropia on the nervous system of frogs. We are induced to publish our observations; for though in the main they are confirmatory of those of previous observers, they differ from them in some respects.

In the first place we will speak of the tetanizing action of atropia. Dr Fraser has shown (1) that in frogs tetanic symptoms follow the subcutaneous injection of a dose of sulphate of atropia equivalent to about 1000th of the weight of the animal; (2) that this tetanus sometimes sets in on the second day, but more frequently on the third, fourth, or fifth; (3) that it varies in its duration from a few hours to seventeen days; (4) that it is due to the action of the drug on the cord (*medulla oblongata* and *medulla spinalis*).

The observations were made during the months of May, June and July. The frogs used for our experiments were with a few exceptions the ordinary *Rana temporaria*. We employed, except when the contrary is stated, a 1 in 20 solution of sulphate of atropia in water, the requisite dose being injected either under the skin of the back or into the axilla. The first twelve cases were observed thrice daily, between seven and eight in the morning, one and two in the afternoon, and five and six in the evening. In the subsequent experiments, observations were made much more frequently, with the view of determining how rapidly paralysis occurred, how soon it reached its height, and how quickly it declined. In some cases the animal was under almost continuous observation for many hours, in others the notes were taken every eight or ten minutes for the first hour, and hourly or every three hours subsequently. We may take this opportunity of explaining that whenever we employ the term

“pithed and pegged” we mean division of the cord by cutting, and destruction of the brain by the introduction of a piece of wood into the cranial cavity. We, like Dr Fraser, often obtained strong tetanus from the subcutaneous injection of atropia, but found that his dose (from $\frac{1}{735}$ to $\frac{1}{1250}$ of the weight of the frog) usually killed our animals instead of producing the desired result. With a smaller dose, however, namely, from $\frac{1}{1500}$ to $\frac{1}{2000}$, we were more successful. The tetanus in our experiments commenced earlier than in Dr Fraser’s, our average period of onset being 20 hours; in one case it was well marked in 3 hours, whilst in the longest delayed it was 28 hours. With us, too, it lasted for a shorter time, for in one animal it continued only eight hours, and never in any instance exceeded five days. We imagine that these differences are due to the time of the year at which the observations were made. In the following table we give a summary of these experiments:—

TABLE I.

Why is the tetanus so long delayed after atropia poisoning? One writer, referring to Dr Fraser’s paper, says that the paralysis of the motor nerves prevents the tetanic condition of the cord from displaying itself on the muscles, but Dr Fraser himself nowhere makes this assertion, and indeed his cases prove the contrary.

This proffered explanation we hold to be erroneous for the following reasons:—

I. Bezold and Bloebaum have shown that even with very large doses it is difficult to destroy completely the conducting power of the motor nerves, and it is obvious that as long as their conductivity is in the smallest degree retained, the tetanic condition of the cord must produce more or less tetanus of the muscles.

II. The onset of tetanus is delayed even in cases in which the dose of atropia is so small as to produce but slight paralysis, and it must be admitted that if the motor nerves are capable of conveying voluntary and normal reflex impressions they can conduct tetanic reflex stimuli. Thus in many of Fraser’s cases there was never complete loss of reflex and voluntary power during the period which elapsed between the injection of the drug and the onset of tetanus. It will be found that of the cases in which he obtained tetanus there were twelve in which

the paralysis was incomplete; that in seven of the thirteen in which it had been complete, a partial recovery of reflex and voluntary power had taken place for a day or more before the onset of the tetanus. In eleven of our own twenty-six cases there was incomplete paralysis of reflex action and voluntary power, and in all these cases the onset of tetanus was delayed. In two cases, indeed, both voluntary and reflex power had been completely regained before the tetanus set in. In one case in which there had been complete paralysis, it began to improve five and a half hours before the commencement of tetanus.

III. If the poison be prevented from having access to certain limited regions by ligature of the nutrient vessels, the onset of tetanus is still delayed even in these protected parts. Fraser gives an account of four experiments, in which he adopted this mode of procedure. In three he tied the femoral vessels, and in one the abdominal aorta, before poisoning the animal, and yet tetanus did not occur in the protected limbs till twenty-two hours, fifty-one hours, three days, and twenty-two hours respectively.

We have tested the action of atropia on ten pithed and pegged frogs, in which, before poisoning, the abdominal aorta had been tied. The following was our mode of procedure:—We first divided the medulla by cutting through the occipito-atlantal membrane, and then passed a pointed wooden peg upwards through the foramen magnum into the skull, so as to destroy the brain. We then placed the animal on its back on the frog-board, and cut through the abdominal wall on one side, usually the left, taking care to avoid the abdominal vein. The intestines were then drawn aside, and the abdominal aorta having been slightly raised, was ligatured just above its bifurcation. The walls of the abdomen were brought together by sutures, and when the animal had recovered from the shock of the operation we injected our sulphate of atropia solution under the skin of the back. At the conclusion of our experiment we always ascertained by a careful post-mortem examination that the vessels had been securely ligatured. In every instance in which more than two or three drops of blood were lost, the operation was deemed unsatisfactory, and the animal rejected.

We give the results of these experiments in the following table:—

TABLE II.—*Observations on Pithed and Pegged Frogs with ligature of the abdominal aorta.*

Number of frog.	Weight in grammes.	Dose of sulphate of atropia in grains.	Proportion between dose and weight of animal.	Degree of tetanus.	Tetanus set in.	Tetanus lasted.	Loss of reflex action begun.	Loss of reflex action at its height.	Degree of loss of reflex action.	
27	32	$\frac{3}{20}$	$\frac{1}{3292}$	Strong	25 hours	52 hours	12 min.	27 min.	Nearly gone	Heart continued beating 3 days.
28	21	$\frac{3}{20}$	$\frac{1}{2160}$	Marked	9 hours	72 hours	12 min.	37 min.	"	"
29	18	$\frac{3}{20}$	$\frac{1}{1851}$	None			20 min.		"	"
30	20	$\frac{3}{20}$	$\frac{1}{2057}$	None			40 min.		"	"
31	18	$\frac{3}{20}$	$\frac{1}{1851}$	None			5 min.	48 min.	"	"
32	20	$\frac{3}{20}$	$\frac{1}{2057}$	None			10 min.	42 min.	Quite lost	"
33	16	$\frac{3}{20}$	$\frac{1}{1646}$	None			5 min.		"	
34	16	$\frac{3}{20}$	$\frac{1}{1646}$	None			5 min.		"	
35	19	$\frac{3}{20}$	$\frac{1}{1954}$	Marked	4½ hours	24 hours	5 min.		"	
							7 min.			Tetanus occurred as early and as marked in anterior as posterior parts of the body.
36	25	$\frac{3}{20}$	$\frac{1}{2572}$	None						
					Average		12 minutes	38 minutes		

It will be seen from the table that in the three cases in which we obtained tetanus it was delayed for 25 hours, 9 hours, and $4\frac{1}{2}$ hours respectively.

In seven cases we tied the femoral vessels in the upper third of the thigh. Our mode of procedure was as follows:—We pithed and pegged the animal in the usual way, and having placed it in a prone position, carried an incision through the skin on the outer side of the thigh, when the vein coming into view was readily secured. By gently separating the muscles the artery was then seen and was tied as near the abdomen as possible, care being taken not to touch or otherwise injure the nerve. Finally the skin was brought together by a few sutures, and the operation was complete. In these cases the fact of the vessel having been securely ligatured was confirmed not only by the post-mortem examination, but usually by comparing by the aid of the microscope the condition of the circulation in the webs of the two feet. The details of these experiments are given in Table III.

It will be seen from the foregoing table that in the three cases in which we obtained tetanus, it occurred simultaneously in the two legs. In two cases it was equal in degree in the two legs, and in the third case it was stronger in the poisoned than in the unpoisoned limb.

We conclude then for these reasons that the late occurrence of tetanus in atropia poisoning is not due to paralysis of the motor nerves, but that it is owing to the cord being slowly affected. It appears that whilst the poison very quickly paralyzes, it takes many hours, or even days, before it tetanizes.

In our experiments we obtained some rather unexpected results. Thus our observations lead us to conclude that atropia paralyzes much more through its depressing action on the spinal cord than on the motor nerves. It is well known that considerable difference of opinion prevails on this point, some experimenters attributing the paralysis chiefly to the action of the poison on the motor nerves, and others to its action on the cord. Fraser in his article "On the connection between Chemical Constitution and Physiological Action," Part II, says, atropia "produces paralysis chiefly by affecting

the motor centres and sensory nerves," and our observations confirm this conclusion in respect of the motor centres (spinal cord).

Thus in the experiments we have recorded in this paper, after tying the abdominal aorta, or the femoral artery and vein, and then poisoning the animal, we found that paralysis set in as early, progressed as quickly, and became as complete in the ligatured as in the unligatured, and consequently poisoned limb.

It occurred to us that perhaps our experiments were made at a different time of year to those performed by other observers, and that this might account for the difference in our results. Our first observations were made in May, June and July, but with the view of solving the point we repeated many of them during the month of November. We tied the femoral artery and vein of the right leg of two frogs, and then poisoned them by injecting sulphate of atropia under the skin of the left axilla. To one we gave a dose too small to produce complete paralysis; to the other a much larger dose, namely half a grain, which caused complete paralysis in two minutes. In the frog to which the small dose had been administered, both posterior limbs were almost completely paralysed, but the ligatured limb was a little the stronger after the poisoning. In the frog with the large dose, both hind limbs were absolutely paralysed in two minutes. We feel bound, therefore, to conclude that sulphate of atropia paralyses in great part by its action on the spinal cord.

Does atropia exert its action directly on the cord, or only indirectly through its influence on the heart and circulation? Is it a spinal depressant, or are the phenomena we have witnessed simply due to its action as a cardiac poison?

Atropia powerfully depresses the heart, slowing or even completely arresting its action. Even in cases in which the number of pulsations is reduced by only a half the heart does very little work, for on examination it is found that during diastole it becomes but slightly distended with blood, so that the circulation must be in reality almost at a standstill. That such is the case is also shown by a microscopic examination of the web of the foot, when the blood will be seen to be either

stationary, or to be moving very slowly in a few only of the larger vessels. It occurred to us, this effect on the heart and circulation might cause the paralysis of the spinal cord.

Vulpian found that ligature of the aorta just above the heart suspended, in the course of a few hours, the excitability of the cord, and soon after impaired the conductivity of the motor nerves. The paralysis from atropia poisoning, however, comes on very much more quickly than this, a circumstance which at first sight appeared at once to solve the question, and to show that atropia exerts a specific, or primary action on the cord. It occurred to us, however, that it was not improbable that in summer when nutrient changes in frogs are performed much more rapidly than in winter, the functional activity of the cord might be sooner affected by arrest of the circulation. We determined, therefore, to repeat Vulpian's experiment in a modified form. We tested the condition of reflex action and voluntary movement in eight frogs, in which the circulation had been arrested by mechanical means. In two of these cases the heart was cut or torn out from the chest, and in the remaining six the aortæ were securely ligatured just above their origin from the bulb. The latter operation was performed as follows:—The animal was pithed by cutting across the medulla, and pushing a spigot of wood through the foramen magnum into the cranial cavity. When the effects of the shock had completely passed off, we pinned the (brainless) animal down on its back, and opened the thorax, by elevating the lower end of the sternum and cutting through the adjacent soft tissues. The heart was then seen beating, and the pericardium having been opened, no difficulty was experienced in slipping a ligature under the aortæ close to the bulb, and tying them simultaneously. Finally, the sternum was replaced, and the edges of the incision were brought together with a few sutures. The operation was usually performed in a very few minutes, and in most cases not a single drop of blood was lost. The experiment of arresting the circulation by removing the heart was even simpler. The brain having been destroyed as before, the thorax was opened by one cut of the scissors and the heart was seized in the forceps, and at once removed. We may mention that the success of the operation was confirmed

by a post-mortem examination, although such a step may hardly appear to have been necessary.

As the result of these experiments, we found that, on an average, the impairment of reflex action commenced in 13 minutes, and that the paralysis was complete in 37 minutes. It will be seen that our results differ considerably from those of Vulpian, a discrepancy which we then thought might possibly have been due to the season, and the condition of functional activity of the frogs, although our subsequent experiments have shown that such is not the case. As our experiments on circulation were made at the same time, and under identically the same conditions as our observations on atropia, they are obviously the best fitted for purposes of comparison.

By reference to the table (Table II.) giving the results of poisoning by atropia in frogs in which the lower limbs had been protected by ligature of the abdominal aorta, it will be seen that in four of these cases loss of reflex action was complete on an average in 38 minutes. These results accord in the most striking manner with those already described as resulting from the mechanical arrest of circulation, and they might be considered to afford a strong proof that the cardiac action of atropia is sufficient to account for the paralysis of the cord produced by this drug. Such, however, is not the case, for on examining the table it will be found that our experiments are in some respects unsatisfactory. The dose of atropia administered was small, so small, in fact, that in two cases the paralysis was never complete. It was therefore obviously necessary to ascertain whether larger doses would not produce complete paralysis in a shorter time. The experiments necessary for the elucidation of this point were made in November, and the opportunity was taken of instituting a series of comparative observations with the view of determining the effects of mechanical arrest of circulation in producing complete paralysis in brainless frogs. These results are given in the accompanying table :—

EFFECTS OF SULPHATE OF ATROPIA.

Pithed and Pegged Frogs poisoned with Atropia.

Date.	Weight of frog.	Amount in grains of sulphate of atropia.	Proportionate dose.	Paralysis complete.
Nov. 29	20 grammes	$\frac{1}{3}$	$\frac{1}{6\frac{1}{7}}$	2 minutes
"	24 "	$\frac{3}{5}$	$\frac{1}{6\frac{1}{7}}$	4 minutes
"	30 "	$\frac{3}{10}$	$\frac{1}{15\frac{4}{3}}$	9 minutes
"	20 "	$\frac{1}{5}$	$\frac{1}{15\frac{4}{3}}$	3 minutes
Average				4.5 minutes

Table showing the effect of mechanical arrest of circulation in pithed and pegged frogs.

Nov. 29			24 minutes
"			55 minutes
"			24 minutes
Average			34 minutes

In these observations, sulphate of atropia caused, on an average, complete paralysis in 4.5 minutes, whilst mechanical arrest of the circulation required, on an average, 34 minutes. In the first of the atropia cases recorded in this table, we tied the femoral vessels before poisoning, and yet the paralysis became complete in both posterior limbs in 2 minutes.

We conclude, then, that atropia has a direct paralysing action on the cord, and does not affect it through its depressing action on the circulation.

In a paper in the volume of the *Medico-Chirurgical Transactions* for 1876, we have endeavoured to show that tetanus is not due to stimulation or an excited condition of the cord, but to a diminution or loss of resistive force in the reflex portion of the cord. This resistive force localizes the impressions conveyed through the nerves to the central nervous system, and when it is destroyed an impression can diffuse itself throughout the cord and produce a general evolution of force, which being conveyed by all the motor nerves to every muscle, produces tetanus.

We believe that the action of atropia confirms this view, or

at least is strongly opposed to the current notion that tetanus is due to an excited condition of the cord. Thus atropia, we believe, depresses the cord very powerfully. The resulting paralysis, which after moderate doses passes off in the course of a few hours, is followed by tetanus, sometimes in twenty-four hours, and at others much later. Now it appears to us almost inconceivable that a remedy should first paralyse the cord and then many hours later stimulate it. It may be urged that this delay in the appearance of the tetanus depends on the primary depression of the cord, and that the tetanus cannot occur till the paralysis has disappeared. This objection is obviously insufficient, for after a small dose of atropia the partial paralysis ceases in a few hours, or even in an hour, and the animal then seems quite well, but nevertheless the tetanus is delayed for twenty-four or more hours. Again, if this explanation is true, then the tetanus should never occur till the paralysis has disappeared, but this, though generally true, is not always the case, especially in frogs pithed and pegged before poisoning; for in these animals it often happens that paralysis, though far from complete, continues, and after some hours tetanus supervenes, at first very slight, so that a strong irritation excites tetanus, but a weaker irritation a coordinated reflex act. If tetanus depends on a stimulated condition of the cord, coordinated reflex acts should improve on the onset and with the increase in the amount of tetanus, but in reality the very reverse happens, for as tetanus grows stronger, coordinated reflex action simultaneously grows weaker and weaker.

Again, when unmutilated frogs made tetanic with atropia die, the tetanus continues to the last, growing weaker and weaker. This is still better seen in pithed and pegged frogs, for in them the tetanus also continues till all reflex action ceases. Now if tetanus depends on a stimulated condition of the spinal cord, it is obvious that as the cord gradually dies and consequently its functions become depressed, tetanus should cease, and give way to normal coordinated reflex action, but this does not happen; for on the contrary the tetanus grows weaker and weaker, still however, persisting until all reflex action becomes extinct. We have thus in atropia a drug that in large doses produces in pithed and pegged frogs progressive loss of power in the

cord, then after 24 or more hours tetanus sets in, which gradually increases in severity, coordinated reflex action simultaneously declining. We have, indeed, according to prevailing views a drug which paralyses the cord, and then after many hours the paralysis continuing or progressing it stimulates the cord.

When the paralysis is only slight, or when the animal completely recovers from it, then tetanic contractions of the muscles far exceed the amount of muscular action occurring in a natural coordinated reflex act; that is to say, during the tetanic paroxysm, there occurs a far greater discharge of nervous force in the cord than occurs in a normal coordinated reflex act, and this fact might be thought sufficient to justify the term stimulation of the cord. We have, however, already shown elsewhere that this view is probably incorrect.

When the paralysis is considerable and continues till the tetanus supervenes, the tetanic contractions are slight and the discharge of nervous force in the cord is probably less than occurs in a natural coordinated reflex act, and we have then paralysis with weak tetanus. The explanation of this combination is that atropia paralyses the reflex function as well as the resistive power of the cord. The paralysis of the reflex function of course weakens reflex action, whilst the paralysis of the resistive power allows a stimulus to spread throughout the reflex region of the cord, and hence every muscle becomes contracted and tetanus is produced; but as the reflex function is depressed the tetanus is weak.

In atropia we have a drug which quickly paralyses the reflex function of the cord, but requires a much longer time to diminish the resistive power of the cord; hence paralysis precedes and may even disappear some hours before the onset of tetanus.

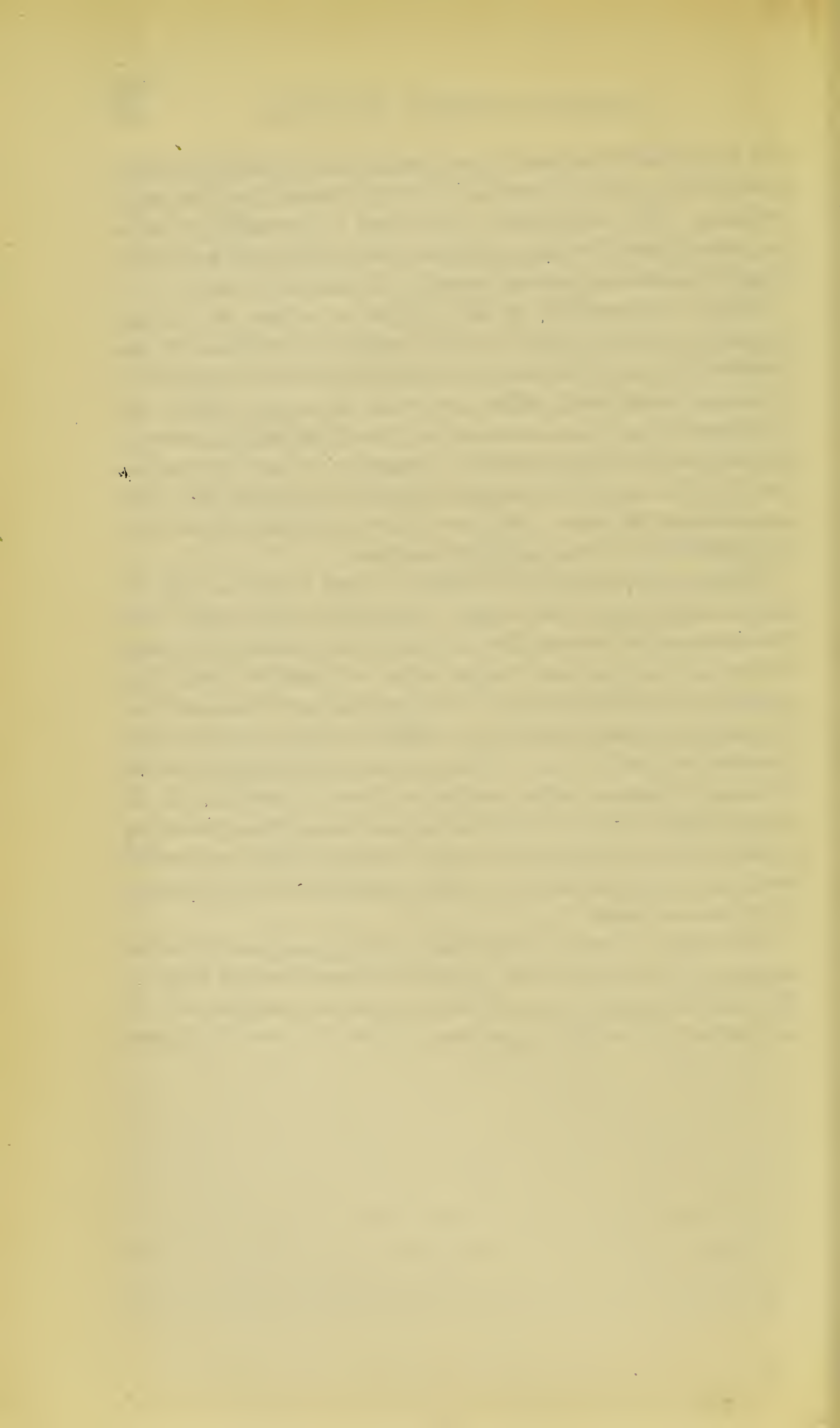


TABLE I.—*Effects on Frogs of Subcutaneous Injection of Atropia.*

Number of frog.	Weight in grammes.	Dose of sulphuric acid in grains.	Proportion between dose of atropia and weight of animal.	Degree of tetanus.	Tetanus lasted.	Tetanus first appeared.	Loss of reflex action.	Remarks.
1	17	20	$\frac{1}{175}$	Very strong	4 days	25 hours	Complete	Recovered. Tetanus increased as animal regained reflex power.
2	21	20	$\frac{1}{112}$	None			Complete	Died.
3	20	21	$\frac{1}{100}$	None			Complete	Animals kept till rigor mortis and putrefaction set in.
4	26	20	$\frac{1}{116}$	None			Complete	Died.
5	21	20	$\frac{1}{116}$	None			Complete	Died.
6	24	20	$\frac{1}{118}$	Strong	5 days 3 days	22 hours 11 hours	Complete	Recovered. Tetanus begun before return of voluntary or reflex power.
7				Slight			Complete	Died. Never any return of voluntary or reflex power.
8				Slight		3 hours	Complete	Died. Up to time tetanus set in there was a fair amount of voluntary and reflex power.
9				Marked		24 hours	Incomplete	Recovered. Good reflex and voluntary power all tetanus set in.
10				"	40 hours	28 hours	Incomplete	Recovered. Good reflex and voluntary power all tetanus set in.
11				"	29 hours	23 hours	Incomplete	Recovered. Good reflex and voluntary power all tetanus set in.
12				None			Complete	Recovered. Paralysis slowly increased for 3 hours and then improved and almost recovered in 8 hours more.
13	20	$\frac{3}{16}$	$\frac{3}{112}$	None			Incomplete	Recovered. Paralysis increased for 2 hours; almost recovered in 6 hours more.
14	19	$\frac{1}{16}$	$\frac{1}{100}$	None			Incomplete	Escaped. Paralysis begun in 6 minutes; at height in 15 to 30 minutes; began to improve 24 hours.
15								Recovered. Paralysis begun in 7 minutes; at height 15 minutes; began to improve 24 hours.
16	19	$\frac{1}{16}$	$\frac{1}{112}$	Slight	30 hours	24 hours	Incomplete	Escaped. Paralysis begun in 8 minutes; at height in 15 minutes; began to improve 3 hours.
17							Incomplete	Recovered. Paralysis begun in 8 minutes; at height 16 minutes; began to improve 54 hours.
18	14	$\frac{1}{16}$	$\frac{1}{160}$	Marked	30 hours	24 hours	Incomplete	Recovered. Paralysis begun in 8 minutes; at height 16 minutes; began to improve 54 hours.
19	18	$\frac{1}{16}$	$\frac{1}{117}$	Slight	11 hours	24 hours	Incomplete	Recovered. Paralysis begun in 10 minutes; at height 30 minutes; began to improve 24 hours. Completely regained voluntary and reflex power before tetanus set in.
20	17	$\frac{1}{16}$	$\frac{1}{100}$	Slight	24 hours	24 hours	Incomplete	Recovered. Paralysis begun 16 minutes; at height 27 minutes; began to improve 24 hours. Regained voluntary and reflex power before tetanus set in.
21	18	$\frac{3}{16}$	$\frac{1}{111}$	Strong	8 hours	24 hours	Incomplete	Recovered. Paralysis begun 9 minutes; at height 30 minutes; began to improve 2 hours. Almost recovered before tetanus set in.
22	15	$\frac{3}{16}$	$\frac{1}{112}$	None			Incomplete	Recovered. Paralysis begun in 8 minutes; at height 34 minutes; began to improve 14 hours.
23	12	$\frac{3}{16}$	$\frac{1}{111}$	Very strong	67 hours	11 hours	Complete	Recovered. Paralysis begun 8 minutes; at height 20 minutes; began to improve 54 hours.

TABLE III.—*Femoral Artery tied in upper third of thigh.*

	Number of frog.	Weight in grammes.	Dose of sulphate of atropia in grains.	Proportion to weight of animal.	Tetanus.	Tetanus lasted.	Tetanus first appeared.	Loss of reflex action begun.	Loss of reflex action at its height.	Degree of loss of reflex action.	
37	16	$\frac{15}{100}$	$\frac{1}{100}$	$\frac{1}{100}$	Slight	10 hours	23 hours	3 min.	51 min.	Almost complete	Left femoral artery tied. Soon after poisoning left leg noticed to be a little the weaker. In the middle of the day began to improve and had nearly recovered by the evening; the right leg always remaining rather the better. Tetanus always equal in both legs and began in both at the same time.
38	19	$\frac{25}{100}$	$\frac{1}{100}$	$\frac{1}{100}$	None			10 min.		Almost complete	Artery and vein of right leg tied. The left leg was always the stronger both as paralysis progressed and again improved. Paralysis in protected leg became quite complete.
39	20	$\frac{25}{100}$	$\frac{1}{100}$	$\frac{1}{100}$				3 min.	38 min.	Almost complete	Right femoral artery and vein tied. Solution of atropia injected under skin of axilla. Reflex action and voluntary power equal in both legs till after 24 hours, when the right leg became rather the weaker.
40	22	$\frac{1}{100}$	$\frac{1}{100}$	$\frac{1}{100}$	None			10 min.		Complete	Right femoral artery and vein tied. Reflex action and voluntary power remained equal in both legs after poisoning.
41	23	$\frac{1}{100}$	$\frac{1}{100}$	$\frac{1}{100}$	Strong	24 hours	13 hours				Right femoral artery and vein tied. Immediately after the ligature noticed the voluntary and reflex power were decidedly less in the ligatured leg, and continued so. Tetanus always stronger in the left (unprotected) limb. Began at the same time in both limbs. Irritation of any part of the body excites it.
42	31	$\frac{1}{100}$	$\frac{1}{100}$	$\frac{1}{100}$	Slight	5 hours	23 hours	5 min.	10 min.	Incomplete	Reflex action and vein tied. Reflex action and voluntary power weaker in the protected than unprotected limb. Tetanus began at the same time in both hind limbs, and was equal in both.
43	19	$\frac{1}{100}$	$\frac{1}{100}$	$\frac{1}{100}$	None			2 min. 5 min.	10 min. 5 min.	Complete	Right femoral artery and vein tied. Reflex action and voluntary movement, before and after poisoning, weaker in the right leg.

FURTHER OBSERVATIONS AND EXPERIMENTS REGARDING THE TRUE NATURE OF TETANUS.

By SYDNEY RINGER, M.D., *Professor of Therapeutics at University College*, and WILLIAM MURRELL, L.R.C.P., *Medical Registrar at Westminster Hospital*.

IN a paper published in the *Medico-Chirurgical Transactions* for 1876, we controverted the view commonly accepted that tetanus is always due to increased excitability of the spinal cord, and we detailed numerous experiments to prove that in tetanus the resistance of the cord is diminished or destroyed, so that an impression conveyed by an afferent nerve can spread throughout the reflex portion of the central nervous system and produce tetanus. Many persons having expressed strong doubt as to the existence of this "resistance," we propose now to give the reasons for our belief in this property, and to shew that it is not fixed, nor unmodifiable, but that probably disease, certainly some drugs, will weaken or destroy it, the other functions of the cord meanwhile remaining unimpaired or but slightly depressed.

We first draw attention to the fact that this resistance is recognised in recent works on Physiology. Thus Hermann says, resistance of the cord is lessened in tetanus, and Ferrier, that in strychnia tetanus "the resistance to radiation is diminished." This view, however, is more definitely and more cogently propounded by Dr Michael Foster, than by any other physiologist with whom we are acquainted. In his recent *Text Book of Physiology* he explains in the most luminous way the part which "resistance" plays in nervous phenomena¹.

¹ Whilst this paper is in the press, our attention has been called to Bernstein's *Nerven und Muskel-Systeme*, 1871. In Section iv. he arrives at very similar conclusions to those we have expressed in the paper already referred to. He says, "Physiological facts point to the conclusion that there is a connection of the sensory centres with one another," "for a phenomenon which forcibly points to such a connection, is that of irradiation. It is known that if a sensation is increased so as to become pain, it will not confine itself to the spot which has been irritated; the whole hand, nay, the whole arm, may ache, if the cause of the pain is only in a finger. It even happens that in such a case we feel the same sensation of pain in the corresponding finger of the other hand, though in a less degree. This phenomenon can only be explained by peculiar arrangements and processes in the perceiving central organs." "But it will be asked,

We were unaware till after writing our paper that this property of the cord was recognised; when, on referring to Hermann's *Physiology*, we found it mentioned there, and we adopted his expression "resistance" instead of the term "increased diffusibility" we had devised for ourselves.

Most writers consider tetanus to be due simply to increased excitability of the cord; indeed, in most works on Therapeutics it is taken for granted that tetanus is evidence of increased excitability of the cord.

Those writers who attribute tetanus simply to increased excitability of the cord imply the existence of resistance, though they do not appear to recognise the necessity for such a property. According to their view, in traumatic tetanus, and in strychnia tetanus, the reflex function of the spinal cord is greatly heightened, so that a slight irritation sets free in the cord an excessive discharge of nervous force, so strong indeed that overstepping the part of the cord functionally connected with the irritated nerve, it may spread, and excite a discharge of force throughout the cord. In other words, they believe that in health a discharge of force is restricted within certain areas of the cord producing co-ordinated action, but in an excited tetanic cord, the resistance limiting the discharge to certain areas is overcome, and the stimulation radiates throughout the reflex portion of the nervous system. This view, therefore, whilst implying a resistance or limiting force, in the central nervous system, possible however to be overcome, implies that this resistance is a constant force incapable of being heightened or depressed by disease or medicines.

Our observations in the paper previously referred to, show that in the tetanus induced by *Buxus Sempervirens*, and by *Gelseminum*, the diminution or destruction of the resistance

why do only strong impressions cause irradiation, and why not also weak ones? and then, why does not irradiation extend over the whole sensory centre; whereas it occupies only part of it? We are hereby led to an assumption which we shall render probable also by other reasons; namely, that the excitation has to overcome resistance in the ganglionic cells, and, on account of it, undergoes a loss in its intensity." Not only may impressions radiate in sensory centres, but "it also happens that the pain may cause reflex cramps. Then the stimulus is so great that in spreading out through the neighbouring sensory centres it is not yet reduced to its liminal value, and it then enters motor centres, first of all such as are situated on the same level with the irritated sensory centres and the spinal cord." Speaking of strychnia tetanus, he says, "It is simply due to a depression of this resistance in the nervous centres."

is the sole cause of the tetanus. To make ourselves clear we draw attention to the fact that both box and gelseminum are powerful depressors of the reflex function of the spinal cord, and that in full doses they soon produce complete paralysis of the cord.

In a frog poisoned by either drug we get first great weakness; the animal hops with difficulty, or perhaps can barely crawl, effects due to the action of the poison on the spinal cord, then tetanus supervenes. But the tetanic paroxysms, though very distinct, are in many instances slight. At one period we can get either a normal co-ordinated action or tetanus, according to the degree of stimulation, a weak stimulus producing a co-ordinated reflex act, a stronger stimulus, tetanus. At this time, as the tetanus grows stronger, the normal co-ordinated reflex action is growing weaker; and after a short time, tetanus also grows weaker, and ultimately slowly declines, till at last it is expressed only by slight quivering in all the muscles of the body. Now here we maintain that at the onset of the tetanus there is no increased excitability of the cord, but the very reverse state—paralysis: for the tetanus is preceded by paralysis of the cord. As the tetanus becomes more marked, normal co-ordinated action grows less, shewing that paralysis of the cord is progressing; and at last tetanus itself becomes excessively feeble, shewing that the cord is almost exhausted and paralysed. If then we have no increased excitability, how does it happen that an impression, say to the tip of one toe, after reaching the cord is not restricted to its proper portion of the cord, but diffuses itself throughout it, causing a general, but weak, evolution of nervous force, and consequently a weak, but general, contraction of the muscles, that is to say, tetanus? This can be only explained on the supposition that some change has taken place in the cord, whereby a stimulus is no longer confined to a part of the cord, but can diffuse itself; that some restraining or localizing influence is reduced or destroyed, and to this is given the name “resistance.”

Further, we found that in brainless frogs after two or more days, when reflex action had begun to decline, on striking the animal between the shoulders we induced tetanus, and as co-ordinated reflex action grew weaker, the tetanus meanwhile

became stronger, and was more easily induced; and in some cases, a few hours before the cessation of reflex action we excited strong tetanus lasting half a minute to a minute, the animal becoming rigid from the powerful muscular contractions. Now we submit that in these cases the tetanus could not be due to increased excitability, unless it is maintained that the operation excited inflammation of the meninges of the cord, a supposition highly improbable, for various reasons. We maintain that the tetanus is due to diminution of the resistance in the dying cord, enabling a powerful stimulus, as a blow on the trunk, to spread throughout the cord, and produce tetanus. For further details we must refer the reader to the paper we have mentioned.

We now record some additional observations we have lately made. These we think conclusively prove that tetanus is not always due to increased excitability of the cord. These observations, too, constrain us to admit a resistive power susceptible of modification, the other functions of the cord remaining but little or not at all affected. We pithed¹ and destroyed the brain of three frogs, and then watched for the decline of reflex action. On the third day this was much weaker; in one frog so weak that, on pinching a toe, it only feebly withdrew its legs. We then injected under the skin of the back $\frac{1}{1500}$ grain of strychnia, which in about half an hour induced tetanus. This was very weak in the frog whose reflex action was nearly annulled, and the tetanus in this instance, though distinct, was feebler than the amount of muscular force developed in a normal vigorous reflex act; in other words, the reflex act, though tetanic, was weak.

In the other two frogs, with reflex power much less weak before the injection, we induced strong tetanic convulsions on the slightest irritation, or even shaking the table, the paroxysms lasting a minute or longer. Next day, however, the tetanus was much weaker, and about equal to the tetanus induced by strychnia in the frog with very weak reflex power. The tetanus grew weaker and weaker, but persisted till all reflex action became extinct; and for some time before this, the muscular

¹ Perhaps it is hardly necessary to say that by the term pithed we mean division of the cord opposite the occipito-atlantal membrane.

force displayed after stimulation was far less marked than that occurring in a normal co-ordinated reflex act. We again had weak tetanus excited in a weak and dying cord. These experiments we several times repeated.

Now we venture to maintain that it is impossible to explain this tetanus otherwise than on the supposition of a resistive force, which the strychnia weakened or destroyed. It certainly cannot be explained on the supposition that strychnia simply produces increased excitability of the cord. We are not now denying that strychnia may "excite" or "stimulate" the cord, but admitting this, the tetanus we have just described cannot be due merely to this increased excitability; for were this so, the strychnia should have first improved, then completely restored normal co-ordinated reflex action, and then, on the cord becoming still more "stimulated," tetanus ought to have supervened.

It may be objected that with brainless frogs in a few hours or in two or three days the afferent and efferent nerves become depressed as well as the spinal cord; and hence, though strychnia may restore the lost functional activity to the cord, yet as the impression conveyed thereto is weakened, and the conductivity of the motor nerves is also depressed, the tetanus itself ought to be very weak. We therefore devised the following experiment:—We pithed and pegged a frog, and after tying the femoral vessels of the right leg close to the trunk, we injected into the abdominal cavity a mixture containing one grain of extract of Calabar bean, and $\frac{1}{120}$ grain of strychnia. The Calabar bean we used to depress the cord, and as we wished to induce depression of the cord without effecting any alteration in the afferent or efferent nerves, we tied the vessels of the right leg, thus protecting the tissues below the ligature from the effect of the drug. In twelve minutes slight tetanus set in, the legs on strong mechanical irritation being powerfully shot out once, and once only, after each stimulation. Co-ordinated and tetanic reflex action persisted simultaneously; that is, a weak stimulus excited co-ordinated action, a stronger, the tetanic extension of the legs just described. The co-ordinated reflex action grew weaker and weaker, the tetanus at first remaining undiminished, then it also declined. In this

experiment the action of the Calabar bean at once reduced the cord to the same condition as in a frog which has been pithed two or three days, but of course without depressing either the afferent or efferent nerves of the ligatured leg.

Our argument is otherwise strikingly supported. In brainless frogs (frogs pithed and pegged) reflex action often declines much more quickly in one hind leg than in the other. To a moderate sized frog with very unequal power in the hind legs, one leg being rather vigorously withdrawn on irritating its toes, whilst the other was only partly withdrawn, we injected under the skin of the back $\frac{1}{1500}$ grain of sulphate of strychnia. In half an hour slight tetanus set in, first in the weaker leg, being for some time decidedly stronger in this leg. Now if strychnia tetanus is simply due to "stimulation," in other words to increased excitability of the cord, then the tetanus should certainly have first shown itself in the stronger leg, as it would naturally require less stimulation to induce tetanus in this than in the weaker limb. We noticed also that at a time when the tetanus was so slight that we doubted if it were present, by exercising the limbs and thus weakening co-ordinated action we induced decided tetanus, which rest again weakened, at the same time strengthening co-ordinated action, and strong tetanus could be again induced by a second time weakening the cord by exercising the limb. Now were strychnia tetanus due simply to "stimulation" (increased excitability), it is obvious that the very reverse should have happened.

A similar fact is often witnessed in disease, when paralysed limbs sooner become tetanized by strychnia than other parts of the body, as in the case of hemiplegia from brain disease. Here half the cord is not exercised at all or but slightly, and consequently its nutrition becomes defective, and it wastes. Strychnia will induce tetanus more readily in this depressed half of the cord than in the opposite healthy half.

But it may be said we admit a resistive force which may be overcome, and as the cord dies—as the reflex function diminishes—this resistance will *pari passu* decline; so that with a slight improvement of the reflex function, the evolution of nervous force in one part of the cord will overpower the weakened resistance, and spread throughout the cord. This position

concedes at once that the resistance is alterable in amount, thus admitting a part of our contention. But the explanation in question is altogether inadequate to explain the very different effects of paralyzers of the cord. Thus to compare three drugs—Physostigma, Gelseminum, and Box: Physostigma paralyzes the cord without producing tetanus; Gelseminum paralyzes the cord, and produces weak tetanus; Box paralyzes the cord, and excites strong tetanus. How are we to interpret these different effects? Why do Box and Gelseminum tetanize, and not Physostigma? Why should Box tetanize far more than Gelseminum? Before attempting to explain this apparent anomaly, we must interpose two preliminary considerations:—

1. That tetanus is producible only in two ways, either by increasing the excitability of the reflex function, so that the evolution of force may be sufficient to overcome the normal “resistance,” and spread throughout the cord; or the “resistance” itself being diminished, an impression conducted to a cord with its reflex function in a normal or even in a depressed state, can overcome the weakened resistance, and affect the whole reflex portion of the cord.

2. It is quite inconceivable that a drug should simultaneously both depress and stimulate (increase excitability of) the same function.

Now, Gelseminum and Box, whilst they both tetanize the cord, depress at the same time the reflex function, and consequently cannot possibly produce tetanus by “stimulating” the cord. Their tetanizing action therefore can be explained solely by their power to diminish “resistance.” The difference in the amount of tetanus, produced respectively by Gelseminum and Box, we explain by inferring, that Gelseminum which induces considerable cord paralysis with weak tetanus, exerts a greater effect on the “resistance” than on the reflex function, and the difference being but slight, we get weak tetanus. Box produces cord depression with much stronger tetanus, showing that the drug exerts an effect far greater on the resistance than on the reflex function; and the resistance being greatly weakened before the reflex function is much

depressed, tetanus excited by Box is far stronger than that from Gelseminum.

Granting therefore that whatever depresses the cord will diminish resistance, we must admit, that some remedies manifest a greater power over resistance than over the reflex function; and when the depression of resistance is greater than the depression of reflex action, we get tetanus. The relative effect on the reflex and the resistive functions well explain the various degrees of paralysis associated with tetanus, and the strength or weakness of the tetanus itself.

We would suggest that conceivably we may have four combinations in tetanus.

1. Tetanus with increased excitability and normal resistance of the cord.
2. Tetanus with increased excitability, and diminished or destroyed resistance of the cord.
3. Tetanus from mere diminution of resistance.
4. Tetanus with depression of the reflex function and diminished resistance.

We have adduced in this paper sufficient evidence of the fourth form of tetanus, and have elsewhere expressed a doubt if the first and second kinds of tetanus ever occur.

Surely, it will be said, the strong tetanus of strychnia must be due to increased excitability of the cord, as well as diminution of resistance; for in a paroxysm, induced by even a slight irritation, the amount of muscular force, and *ergo* of the nervous force developed in the cord, is far greater than occurs in a normal co-ordinated reflex act, and this excessive evolution of force proves the increased excitability of the cord. But we think that strychnia tetanus is best explained by simply temporary diminution or abolition of resistance. For we have shown in the pamphlet already referred to, that loss of resistance, even with depression of the reflex function, will produce strong tetanus. This is the case with Box. This drug, as we have seen, produces first partial cord paralysis; then strong tetanus ensues, whilst the co-ordinated reflex contractions, which can be induced by weak stimulation, are at the same time

growing progressively weaker; that is to say, we get strong tetanus with progressive cord paralysis.

In order to explain these strong paroxysms when the evolution of nerve force is far greater than that occurring in a normal co-ordinated act, it is obvious we must assume that the resistance not only restricts impressions to certain areas of the cord, but that it also limits the amount of force evolved; in fact, by paralysing "resistance" we not only allow a stimulus to spread throughout the reflex portion of the cord, but also to set free an increased amount of nervous force from every portion of the cord and motor parts of the brain. In other words, the function or condition to which the name "resistance" is given not only localises but restrains reflex action in the spinal cord. If then, in the case of Box, we get strong tetanus with slight depression of the cord, we think it possible that the still stronger tetanus of strychnia may be due simply to depression of this resistive function without any increased excitability. Hence, as in the case of Box, but in even greater degree, a slight stimulation not only spreads throughout the cord, but sets free an excessive amount of nervous force.

It will probably be objected that if diminution of resistance permits also the evolution of an excessive amount of force—that resistance in fact not only localises but restrains or controls the amount of reflex action—then, as resistance becomes weakened, the co-ordinated reflex acts should become stronger; as in that stage of Box and Gelseminum poisoning, when, according to the strength of the irritation, we obtain either a co-ordinated or a tetanic reflex act, the co-ordinated act should become stronger. This is not true of Box and Gelseminum poisoning, probably because, as the tetanus sets in and grows more severe, the paralysis of the cord progresses quickly, so that any increase in normal co-ordinated action due to diminution of resistance would escape detection; though we must grant that this paralysis should likewise weaken the tetanic reflex act. In strychnia poisoning, where there certainly is no weakening of reflex action, the co-ordinated reflex acts on the onset of tetanus do become stronger, as the following observation repeated several times establishes. We pithed and pegged a frog, and when reflex action had considerably declined, but the

limbs were still withdrawn under the stimulus of pinching or electricity, we suspended the brainless animal, by passing a pin through the lips, and pinning it to a retort holder, so that it hung with its legs suspended, and then injected $\frac{1}{1500}$ grain under the skin of the back, and watched for the onset of tetanus. With this small dose tetanus came on slowly, remaining for a long time comparatively weak, so that a slight irritation induced a co-ordinated reflex act; a stronger one, tetanus. In this stage we found that co-ordinated reflex action was much more easily and powerfully induced than before tetanus set in. Thus, before the injection of the strychnia only the irritated leg was withdrawn, and once only, and then again relaxed; but after the setting in of tetanus the leg, in a co-ordinated act, was first withdrawn on slighter irritation; next, as tetanus increased, both legs were withdrawn; and later, both were withdrawn and extended several times, with even a very slight stimulus, as, for instance, the very slightest touch. This effect of strychnia was still better exemplified by the following experiment. A frog, pithed and pegged seventy-one hours beforehand, we suspended by a pin passed through the lips and fixed to a stand, on each side the right ankle we placed the thin wires of the electrodes, tying them to the ankle by waxed thread, then by means of Du Bois Reymond's induction coil we ascertained the weakest current capable of exciting a reflex act. Then we injected $\frac{1}{1500}$ gr. of strychnia under the skin of the back, the instrument standing at 10·5, and as tetanus gradually set in a weaker current was sufficient to produce a co-ordinated reflex act. Thirty-four minutes after the injection, reflex action was induced with the coil standing at 11; in an hour, at 12; in an hour and twenty minutes, at 13; in an hour and a half, at 14; in an hour and forty minutes, at 16. Surely this, an objector might say, is increased excitability of the cord. Of course strychnia so affects the cord that a slight stimulus evokes a very great discharge of nervous force; but the question we raise is this:—Does this increased evolution of nervous force depend on some alteration in the composition of the cord elements, so that chemical changes and consequently the production of force are more easily induced; or is this increase

of force due to weakening or destruction of some controlling power which has been termed "resistance" ?

In support of the theory of resistance, we must again refer to the effect of Box on the cord. This drug first produces cord paralysis, and whilst this quickly advances, strong tetanus occurs, which, as we have said, cannot be due to increased excitability, but must, we think, depend on loss of "resistance" of the cord; and we suggest that it is at least feasible that even the strong tetanus of strychnia may depend simply on loss of resistance, though as the reflex function is in no degree weakened, this tetanus is more powerful than that of Box.

We here adduce some observations confirmatory of this view.

In a brainless frog, after three or four days, reflex action so far declines that it cannot be excited in the smallest degree by stimulation of the extremities; but a sharpish blow over the spine produces slight and general muscular contraction. On repeating the blows, the muscular contraction grows stronger and stronger, at last becoming decidedly tetanic; and now if the blows are still continued, the muscular movements become abolished. These effects we explain in the following way:—The blow on the back diminishes the "resistance" at first very slightly, and though all the muscles are affected they contract but slightly; a repetition of the blows, of the same strength, reduces the resistance more and more, and with each blow a greater amount of nerve force is evoked; that is, the amount of stimulation remaining the same we produce a far greater amount of muscular contraction. Repeating the blows still further, we depress the cord, and at last abolish all reflex action. The increased evolution of nervous force in the cord can be explained, we think, only by the fact of diminished resistance. The augmented evolution of nervous force cannot be due to excitement of the cord, since in this experiment there is nothing to suggest or to explain the increased excitability, and, as we have said, we took care that the blows should be as nearly as possible of the same strength. If this explanation be accepted, then it shows that through diminution of resistance a greater force is evolved with the repetition of a stimulus always of the same strength.

Now if we give a dose of strychnia to a frog in the condition just described, in a short time, when absorption has taken place, we bring the cord of that animal to the condition of the frog which has undergone a repetition of blows on the back ; that is to say, one blow will produce a decided, though weak, tetanic contraction. Here the strychnia acts like the repeated blows, weakening resistance, so that a stimulus will evoke a greater amount of nerve force than would have occurred before the resistance was depressed.

THE INFLUENCE OF SALICINE ON THE HEALTHY BODY WITH SPECIAL REFERENCE TO ITS INFLUENCE ON THE TEMPERATURE. By SYDNEY RINGER, M.D., *Professor of Therapeutics at University College*; and J. S. BURY, *Physicians' Assistant at University College Hospital*.

IN March, 1876, Dr Maclagan, of Dundee, strongly recommended Salicine in acute rheumatism; and in the following April Dr Senator, of Berlin, recommended salicine as a substitute for salicylic acid. As salicine is now largely used to reduce the temperature of febrile diseases, we were induced to undertake a series of observations to ascertain its effect on the temperature in health. Whilst making these experiments we noted carefully, at the same time, the effect of the drug on the various functions of the body; and in this paper we record the results. Before giving our experiments in detail we here point out the results of our observations.

Salicine, as has been pointed out by other observers, acts very much like quinia. Like it, in even large and toxic doses, as large as can be given with safety, salicine depresses the healthy temperature, but in a slight degree, and only for a brief period. Moreover this slight effect follows only the few first doses, and then, in spite of the continued administration of the drug, the temperature quickly recovers its original state.

The slight effect produced by salicine or quinia is well exemplified in the following tables:

Effect of Salicine on Temperature and Pulse.

Boy aged 10.				
Dose.	Temperature depressed.	Depression lasted.	Pulse rose to.	Respiration.
30 grains	0.2	65 min.	Unaffected.	Unaffected.
30 "	no effect		"	"
60 "	0.8	about 2 hrs.	"	"

Quinia.

Boy aged 10.				
10 "	none			
10 "	0.2			
10 "	none			
Girl aged 13.				
8 "	0.2		94	
10 "	none		72	
10 "	none		72	
20 "	0.1	3 h. 15 min.	120	
20 "	0.4	45 min.	98	

These doses of quinia produced marked symptoms of cinchonism. These tables show that like quinia doses of salicine large enough to produce toxic symptoms exert a very slight control over the healthy temperature. The above table regarding quinia is abstracted from a paper published by one of the authors and Mr Gill in the *Medical Times and Gazette*.

In this investigation when a sudden fall, which in a short time is recovered from, occurred in the temperature, we have considered the depression due to some accidental cause as cooling the mouth by exposure or cold drinks, &c., and have not used such observation in our calculations in this paper.

In order to produce any symptoms characteristic of the drug, a single large dose of one dram or more is necessary, or thirty grains repeated hourly, two or three times. Given less frequently, or in smaller doses, it induces no symptoms whatever. Toleration of the drug is soon established, so that at last large doses fail to produce any characteristic effect; though when given at first, without any graduation, these full doses, even after their discontinuance, produce very decided symptoms, which may persist one or two days, and may even become intensified the day after the withdrawal of the medicine. The repetition of large doses may produce slight fever, shown in delaying and greatly lessening the evening normal diurnal fall—an effect probably due to irritation of the stomach.

The aspect of a patient under full medicinal doses is rather characteristic, being in many respects similar to that of a person suffering from cinchonism. The expression is dull and heavy, the face quickly flushes on slight excitement, and the eyes become suffused. The flush, of rather a dusky hue, suffuses itself uniformly over the whole face. The patient, made more or less deaf, often complains of noises in the ears. He complains, too, of frontal headache, and his hands, when held out, tremble a little. His breathing is rather quickened and deepened. In some cases one symptom may predominate; thus deafness may be almost complete, without headache or muscular trembling; but it rarely, if ever, happens that any symptom is unaccompanied with the dull heavy aspect and the readiness to flush.

Under toxic, but not dangerous doses, the headache is often

very severe, so that the patient buries his head in the pillow. There may be very marked muscular weakness and tremor, associated with great muscular irritability, so that a slight tap, say on the shoulder, causes muscular contractions so strong as to jerk the arm backwards. There are often slight spasmodic twitchings when a limb is raised. Tingling of the extremities or other parts of the body sometimes occurs. The voice may become thick and husky. The respiration is hurried, sometimes deepened, sometimes sighing and shallow and almost panting, and seems as though it were performed rather laboriously, but the patient does not complain of any difficulty of breathing. The costal as well as the diaphragmatic movements are involved in the exaggerated breathing. Large doses, often repeated, quicken the pulse to 140 per minute, and it becomes very weak. In these healthy lads the drug did not cause delirium.

It is very noteworthy that salicine renders the sweat neutral or alkaline. We think, too, that the urine becomes neutral or less acid; but on this point our observations are too few to justify our speaking confidently. The alkaline reaction of the sweat we noticed in many rheumatic patients under the influence of large and frequent doses, and the sweat may be alkaline, whilst the urine is acid.

We find that if moderate doses are first given, the medicine may then be increased, till a lad ten years old, beginning with 80 grains, may be brought to take 180 grains daily, without any symptoms.

Though the effect of the drug on the temperature was so slight, we have introduced the charts, because, the observations being made with very great care and at less intervals than in any other observations we know of (excepting some other experiments made by one of the authors and read before the Royal Society), they are, on physiological grounds, valuable as indications of the course the temperature runs throughout the day and the effect on it of food, &c. Moreover on many days no salicine was given.

We tested the effects of salicine in three sets of experiments, each on three healthy lads. To the first two we gave large doses and produced decided symptoms; to the third we

gave at first smaller doses and increased them gradually till he took three drams daily, producing, as we shall see, scarcely any symptoms.

In two sets of experiments the temperature was taken under the tongue ; in the other series, in the rectum. These lads took breakfast between six and seven ; dinner between twelve and half-past, and tea between four and five.

We took the temperature hourly, from 9 a.m. till 12 p.m. Observations were made hourly for six days on the first lad ; on the second for eight days ; on the third for thirty days. For a few days we gave no salicine, that we might compare the temperature of the body on salicine days with non-salicine days.

Our first set of experiments were made on a lad aged ten, weighing $44\frac{1}{2}$ lbs. His temperature was taken under the tongue and during the investigation, he was kept in bed but was allowed to sit up in it. He was admitted with belladonna poisoning, but our observations were not commenced till some days after his complete recovery.

CHART I. MEMORANDA.

Boy aged 10. Weight, 3 st. $2\frac{1}{2}$ lbs. Admitted with Belladonna poisoning Aug. 4.

August 7.

Hour.	Pulse.	Resp.	Remarks.
9	80	20	6 a.m. Breakfast—bread and milk. Thermometer kept under tongue for five minutes.
10	76	20	
11	74	20	9.30. Mug of milk.
12	76	22	12.30. Dinner—mutton, potatoes, rice, bread and milk. Good dinner. Patient kept in bed but allowed to sit up and move about.
1	76	24	
2.15	76	22	
3	76	24	4.30. Tea—milk, bread and butter. Good meal.
4	76	20	
5	72	24	
6	72	22	7.30. Mug of milk.
7	72	24	
8	76	22	
9	72	22	
10	70	16	
11	70	16	
12	68	16	

August 8.

9.15	88	28	7.30. Breakfast—bread and milk.
10	76	24	
11	72	24	11. Mug of milk.
12	72	24	12.30. Dinner—mutton, potatoes, greens, rice pudding, water. Good dinner.
1	78	26	
2.15	78	26	
3	78	24	

INFLUENCE OF SALICINE.

4	76	24	
5	80	26	5·30. Tea—milk, bread and butter, 1 egg.
6	76	24	
7	76	28	7·30. Custard tart and milk.
8	76	22	
9	88	24	
10	80	20	
11	72	18	
12	76	18	12·30. Mug of milk.

August 9.

9	78	22	7·30 a.m. Breakfast—bread and milk. 9 a.m. Amount of urine passed since 9 a.m. yesterday $\frac{3}{2}$ 22.
10	84	24	10 a.m. Mug of milk.
11	80	28	
12	72	28	12·30 p.m. Dinner—mutton, potatoes, no greens, rice pudding, milk. Good dinner.
1	82	28	
2	82	28	
3	80	20	
4	82	24	4·30 p.m. Tea—milk, bread and butter, one egg. Good meal.
5	84	26	
6	88	22	
7	84	24	7·30 p.m. Mug of milk.
8	80	24	
9	72	18	
10	70	16	
11	70	16	
12	72	19	

August 10.

8·45	76	24	5·45 a.m. Breakfast—bread and milk. Good. 9 a.m. Amount of urine passed since 9 a.m. yesterday $\frac{3}{2}$ 22.
9·5	76	24	9·45 a.m. Took 30 grains of Salicine in $\frac{3}{4}$ j of water.
9·20	76	24	10·5 a.m. Thermometer in mouth 10 min.
9·45			10 a.m. Mug of milk. 10. Patient complained of a bitter taste on taking the drug; almost directly after swallowing it, he felt sick and had hard work to keep from vomiting; the sensation of sickness soon passed off. He complained also of frontal headache.
10·5	74	20	10·50 a.m. Took 30 grains of Salicine in $\frac{3}{4}$ j of water.
10·30	76	20	10·50—11·40 a.m. The second dose was followed im- mediately by nausea, which soon passed off; then severe frontal headache came on, so bad that the boy shut his eyes, and buried his face in his arm (this was at 11·10); his face was also much flushed and the conjunctivæ slightly injected. Giddiness, too, experienced.
			At 11·40 these symptoms had almost left him.
12·5	76	24	12·30 p.m. Dinner—mutton, potatoes, rice pudding, milk. Good dinner.
1·10	80	26	
2			
3	76	24	3 p.m. Currant bun.
4	76	24	4·45 p.m. Bread and butter and milk. Good meal.
5	78	25	
6	80	22	5·45 p.m. Sponge cake.
7	82	24	7·30 p.m. Mug of milk and piece of custard.
8	78	24	
9	72	22	
10	68	20	
11	64	18	
12	66	16	

August 11.

8.45	80	24	7.30 a.m. Breakfast—egg and milk and bread and milk.
9.30	76	22	9 a.m. Quantity of urine passed since 9 a.m. yesterday $\frac{3}{20}$.
9.40	76	24	9.40 a.m. 60 grains of Salicine in $\frac{3}{4}$ ij water.
10	76	24	9.52 a.m. Flushed. Complains of frontal headache.
10.15	72	22	9.55 a.m. Headache severe—frontal. Flushes readily.
10.30	72		Dull, heavy, and apparently decided muscular weakness. Tingling, like pins and needles, in right ankle. 11.30. Mug of milk.
10.45	72	24	10.4 a.m. Pain only over left brow. Dull, heavy flushes.
11	76	26	10.7 a.m. Headache getting much better (pupils rather more dilated?)
11.15	70	22	10.15 a.m. Headache only over left brow. Is very dull. Says he feels rather sleepy. Decided muscular weakness. Answers questions slowly. Movement made his head worse. Lies in a semi-stupid state. Is generally very lively. Pulse certainly much softer. Twitchings of leg which he cannot control, and slight of muscles of arm. Lies generally with eyes closed.
12	76	26	10.30 a.m. In much the same state. Still twitchings.
1	72	24	Very dull. Drowsy; lies with eyes closed. No headache. Still flushes very readily. Pulse little fuller and stronger.
2.15	76	24	
3	76	22	
4			
5			
6			
7	80	24	
8	76	24	
9	76	24	10.40 a.m. Drowsiness and dulness not decreased, and still twitches. No headache. Still flushes readily.
10	68	18	10.45 a.m. Still very dull, with decided muscular weakness. Crying, but has no pain. Pulse recovered.
11	68	18	11 a.m. Less dull. No headache or other pain. Still flushes.
12	68	18	11.15 a.m. A little dulness only noticeable.
			12 noon. The boy is lively; looks himself again.
			12.30 p.m. Dinner—mutton, potatoes, bread, milk. Poor dinner.
			4.30 p.m. Tea—bread, butter, milk, jam tart.
			7 p.m. Milk and bread.

August 12.

9	76	24	7 a.m. Breakfast—bread and milk and one egg.
10	76	24	9 a.m. Quantity of urine since 9 a.m. yesterday $\frac{3}{20}$.
11	80	22	
12	76	24	12 noon. Dinner—mutton, potatoes, mug of milk. Poor dinner.
1	80	20	
2	80	24	
3	80	24	
4	68	22	
5			
6	84	24	4.30 p.m. Tea—bread, butter, milk, one egg. Good meal.
7	84	26	7 p.m. Milk and two ginger cakes.
8	84	26	
9	72	18	
10	75	18	
11	68	18	11 p.m. }
12	68	17	12 p.m. } Bedclothes thrown off body and legs.

For the first three days he took no medicine, on the fourth we gave salicine in two doses, each of thirty grains, and on the following day a single sixty-grain dose. Observations were continued throughout the sixth day, although he took none of the drug.

The results of our observations are put into the following table :

	Maximum temperature of day.	Rise after dinner.	Rise after tea.	Evening fall begun.	Diurnal variation.	Average temperature of day.	
1st day	99.1	0.4	0	8	1.6	98.4	No salicine
2nd day	99.5	0.6	0.5	7	1.4	98.7	No salicine
3rd day	99.4	0.4	0.4	6	1.7	98.7	No salicine
4th day	99	0	0	9	1.7	98.3	60 grains in two doses
5th day	99.3	0	0.2	6	1.7	98.5	60 grains in one dose
6th day	99	0	0.2	9	1.9	98.2	No salicine

In respect to this table we must first remark that the rise after dinner and tea lasted a very short time, and we think that part of this rise was due to the warm tea; for after warm drinks we have found that the mouth temperature is often considerably raised, sometimes even to the extent of a degree, remaining so a quarter of an hour or even longer.

A reference to the above table might lead to the conclusion that the effect of salicine was inappreciable or nil, but a glance at the accompanying chart (Chart I.) will show that the drug produced a manifest effect. On the fourth day, after taking three observations at intervals of a quarter of an hour, it will be seen that we administered by the mouth thirty grains of salicine dissolved in water at 9.45, and another thirty-grain dose at 10.50. The medicine produced a decided though slight effect on the temperature. Thus throughout the day, the temperature remained more stationary than on non-salicine days. After the first dose there occurred a fall of 0.2° Fah.; during the next hour it rose 0.4 in spite of the second dose, and the maximum temperature of the day was attained at 11.40. Then instead of rising after dinner and tea, as on the previous non-salicine days, it slowly and continuously declined, so that at 8 p.m. it had fallen 0.4° Fah., then the diurnal variation commenced and amounted to 1.7° Fah. Thus the effect of the salicine on this day was to lower the temperature 0.2° Fah., and to prevent the rise after dinner and tea, effects very slight and unimportant. Next (5th) day, after three observations, we administered in one dose sixty grains of salicine dissolved in two ounces of water at 9.40 a.m. The temperature from this time gradu-

ally fell, reaching its maximum fall of 0.8° at 11, it then rose and had recovered itself at 12, and between 12 and 5 it rose 0.3° ; the evening fall then began and amounted to 1.7° Fah. There was no rise after dinner, and only 0.2° after tea. Thus on this day the effect was a fall of 0.8° , lasting about two hours, and no rise after food. The amount of diurnal variation was unaffected on both the salicine days.

Next day he took no salicine, and his temperature remained remarkably uniform throughout the day, till the diurnal variation set in. The evening fall began between eight and nine, and the diurnal variation amounted to 1.9° Fah.

The drug produced no effect on the pulse or respiration.

Although on each of the two days we gave the same dose, the drug produced far more decided effects after the second than after the first dose. On the first day we gave two thirty-grain doses at sixty-five minutes interval; on the next day sixty grains were given at once. This difference would indicate that the drug is quickly eliminated.

The symptoms produced were slight nausea, probably due to the bitter taste of the drug; then, in a few minutes after the second dose, severe frontal headache set in, so severe that the lad shut his eyes and buried his head in his arm. Flushing of the face especially on any excitement. Slight injection of the conjunctiva, and giddiness. In an hour these symptoms had almost left him, a fact confirming the conclusion that the drug is speedily eliminated.

Sixty grains produced the same symptoms in a more marked degree. Severe headache and flushing came on in twelve minutes. Though a very lively boy, he became very dull and stupid, lying with his eyes closed, and answering questions slowly. He complained of tingling like pins and needles in his right ankle, and suffered from very decided muscular weakness, soon accompanied by muscular twitchings and tremblings of the legs and arms. At this time the pulse was much softer.

In the following table we give the time these symptoms set in and their duration, calculating from the time of taking the medicine.

	Set in.	Ceased.
Headache	12 min.	50 min.
Flushing	12 min. "	1 h. 20 min.
Muscular weakness	15 min.	1 h. 20 min.
Muscular twitchings	35 min.	1 h. 20 min.
Dullness and heaviness	15 min.	1 h. 45 min.

The quantity of urine was almost unaffected, as the following table shows :

	Daily amount.
Without medicine	22 oz.
" "	22 oz.
Salicine day	20 oz.
" "	20 oz.

The next series of observations were made on a lad aged nine, convalescent from pneumonia, his temperature having

become normal ten days previously. We experimented somewhat differently.

The boy was kept in bed. His temperature was taken hourly in the rectum. For two days he took no medicine; on the two following days he took salicine in thirty-grain doses at 10 a.m., 11 a.m., 2 p.m., 3 p.m., 5 p.m., and 6 p.m.; thus in the course of the day he took 3iii. Next day we administered thirty-grain doses eight times ($\frac{3}{4}$ j.), at 10 a.m., 11 a.m., 12 p.m., 1 p.m., 2 p.m., 3 p.m., 4 p.m., and 5 p.m.

The results with this lad are rather singular. On the first day these large doses produced no symptoms, in fact symptoms did not set in till noon of the second day, but they increased during the night, after the discontinuance of the medicine, and were severe all next day, and for three days after.

As in the previous observations, we shall speak first of the effect of the salicine on the temperature, pulse, and respiration.

CHART II. MEMORANDA.

P. B. Aged 9. Convalescent from Pneumonia. Temp. normal on 9th.
September 19.

Hour.	Pulse.	Resp.	Remarks.
9 a.m.	70	22	5·30 a.m. Breakfast—bread and butter, one egg, mug of milk. Moderate breakfast.
10	80	24	10 a.m. Lunch—mug of milk and bread.
11	80	24	
12	80	28	12 noon. Dinner—mutton, potatoes, greens, pudding (rice), mug of milk. Moderate dinner.
1 p.m.	84	24	
2	80	26	
3	70	28	
4	72	28	
5	80	28	5 p.m. Tea—bread and butter, one egg, mug of milk, small bunch of (about 12) grapes. Good meal.
6	80	24	
7	74	24	
8	70	22	} Profuse perspiration of face and upper limbs and chest; lower limbs dry. Face still moist; arms only slightly moist.
9	66	22	
10	66	22	
11	70	18	
12	70	18	

September 20.

9 a.m.	72	24	5·30 a.m. Breakfast—bread, one egg, mug of milk. Moderate breakfast.
10	68	24	
11	68	24	
12	72	20	12 noon. Dinner—mutton, potatoes, greens, milk, pudding (rice). Good dinner.
1 p.m.	68	24	
2			
3	70	24	
4			
5			4·30 p.m. Tea—bread and butter, one egg, mug of milk, and a few grapes.
6	70	24	
7	68	24	
8	68	24	Mug of milk at 7 p.m.
9	60	20	
10	62	20	
11	68	24	
12			

September 21.

9 a.m.	72	26	5.30 a.m. Breakfast—bread and butter, one egg, mug of milk. Good breakfast. Urine $\frac{3}{3}$ XVIII. in last 24 hrs.
9.45			10 a.m. * <i>Salicine gr. xxx.</i> in water $\frac{3}{3}$ I. 10.15. No headache, no heaviness, or any pain or uneasiness.
10.15	68		10.30. No symptoms.
10.30	76	24	11 a.m. <i>Salicine again given in same dose.</i> Boy was repeatedly asked between 11 and 12 if he felt well, and complained of nothing. No alteration in pupils or general aspect of face.
11.15			11.30
12.0	76	28	2 p.m. <i>Salicine gr. xxx. again given.</i> Bowels open once. No symptoms.
1 p.m.	76	28	3 p.m. <i>Salicine gr. xxx. repeated.</i>
1.45			
2.25	78	24	4.15 p.m. Tea—bread and butter, one egg, mug of milk, a few grapes. Very good meal.
3.15			5 p.m. <i>Salicine gr. xxx.</i>
3.45			No symptoms.
4.15			6 p.m. <i>Salicine gr. xxx. repeated.</i>
			No symptoms.
5.15			
5.45			
6.30			
7.30			
8.30			
9.30			
11.0			
12.0			

September 22.

9 a.m.	88	24	5.30 a.m. Breakfast—bread and butter, one egg, mug of milk. Moderate breakfast.
9.45			10 a.m. Took 30 grs. of <i>Salicine</i> in 1 ounce of water.
10.15	88	28	No symptoms. Urine $\frac{3}{3}$ XIII. in last 24 hours.
10.45			Urine slightly acid; contains abundance of <i>Salicine</i> .
11.15			11 a.m. Took 30 grs. of <i>Salicine</i> . No symptoms.
			12 noon. Another dose of <i>Salicine</i> .
11.45			12.15. Dinner—small piece of mutton, little potato, pudding, mug of milk. Very poor dinner. Bowels open 4 times.
12.30			1 p.m. * Another dose of <i>Salicine</i> .
1.15	104	32	1.40 p.m. Tremor of hands when held out. Face flushed, perspiring; looks dull but complains of no headache or pain. Pulse large, soft, compressible.
1.30			2 p.m. Another dose of <i>Salicine</i> .
2.15	108		3 p.m. Another dose of <i>Salicine</i> . 3.15. Much tremor of hands; face flushed.
3.0			4 p.m. Another dose of <i>Salicine</i> . } Face flushed.
3.30	112	32	5 p.m. Repeated. }
4.30			5.15 p.m. Tea—one egg, bread and butter. Very good tea. Marked tremor of the hands whilst eating. Grasp of hands strong and equal.
5.45	116	30	9 p.m. Urine slightly acid. Sp. gr. 1028.
7 p.m.			
8			
9	112	28	
10			
11			
12	108	24	

September 23.

			5 a.m. Boy vomited twice, bringing up remains of food. No breakfast.
9 a.m.	112	32	9 a.m. Looks heavy and dull; is decidedly deafer; can only hear a watch tick when laid <i>on the ear</i> . He feels a tingling in the right ear near the surface; has no buzzing noises in head, no headache, nor pain anywhere. Does not seem to understand questions so well as formerly, and there is a little tremor of lips in speaking and the voice is thick. Breathing laboured and trunk shakes a little during the act. Hands tremble when held out, and small spasmodic movements of the whole upper limb occur at intervals. Also slight jerks and tremor of lower limb when raised from bed.
10	124	32	
11	128	36	
12			
1 p.m.	140	40	9:30 a.m. Feels sick but does not vomit. Grasp of hands is weaker than it was yesterday. Speech a little jerky; voice husky; words not well laid hold of, lips and tongue not being used with natural freedom. Eyes heavy and half shut. Mouth wide open. Rather thirsty. Pulse soft and compressible.
2	128	32	1:30 p.m. Urine neutral; abundance of Salicine. Great muscular irritability, on tapping the muscles they contract. Breathing a little laboured.
3	124	33	4:0 p.m. Pulse of better quality. Symptoms passing off; expression brighter; much less deafness; irritability of muscles as before. No pain anywhere. Manner still dull. Breathing less laboured: more thoracic than diaphragmatic. Much Salicine in urine.
4	120	30	8:0 p.m. Urine slightly acid, contains plenty of Salicine. Less irritability of muscles. Manner still dull, and boy heavy and sleepy.
5	116	32	Dinner at 12 noon of small chop, greens, and potatoes. A moderate dinner.
6	116	32	Tea at 4:15 p.m.—bread and butter, one egg, mug of milk with a little tea in. Very good meal.
7	116	32	
8	116	32	
9	108	26	
10	104	24	
11			
12	96	22	

September 24.

9 a.m.			5:30 a.m. Breakfast—bread and butter, one egg, mug of milk. Good breakfast.
10	100	26	10 a.m. Deafness less. Still looks dull, and unless spoken to, lies with eyes half closed, and very often is asleep.
11	104	28	Muscular irritability still present though less than yesterday, and the muscles contract when tapped. Urine as before.
12			
1 p.m.			3 p.m. Pulse still compressible. Breathing less laboured, but thoracic. Tremor of hands and arms when held out. Slight muscular irritability. Boy looks brighter, and can now hear a watch tick when held at a distance of four inches from the ear.
2	108	24	
3	108	28	
4	94		
5	90		
6	90		
7	90		
8	90		
9	82		
10	82		
11	84	18	12 noon. Dinner—mutton, potatoes, pudding. Moderate dinner.
12			5:15 p.m. Tea—bread and butter, one egg, and mug of milk. Good meal.

September 25.

9 a.m.	74	22	5.30 a.m. Breakfast—bread and butter, one egg, mug of milk. A good breakfast.
10	72	24	One stool at 3 a.m. and a small one at 8 a.m.
11			8.15 a.m. Boy looks much brighter, but his face is very pale. There is still a very little tremor of hands when held out, and just a trace of irritability in the back muscles. Less deafness; eyes less heavy-looking. Urine reaction as before, just tinging blue litmus red; about $\frac{1}{2}$ inch in height in moderate-sized test-tube is coloured deep purple with 1 drop of Liq. Ferri Perchlor.; the colour dissolves on shaking, but 1 drop more of L. F. P. produces a permanent colour.
12	88	26	
1 p.m.			4 p.m. Urine as before. Very slight tremor of hands. Can now hear watch tick when held 1 or 2 feet from head.
2			
3	100		1 p.m. Another stool, making 3 to-day.
4	96		12 noon. Dinner—very small piece of mutton and rice pudding. A very poor dinner.
5	100	24	4 p.m. Tea—bread and butter, one egg, and mug of milk. A good meal.
6			
7	92	22	
8			
9			
10	88	18	
11			
12			

September 26.

			5.30 a.m. Breakfast—bread and butter, one egg, mug of milk.
9 a.m.	88	22	9 a.m. Free from dulness and deafness, can hear a watch tick at a distance of 3 feet from head, an improvement even on yesterday. No tremor or muscular irritability.
10	76	22	Urine slightly acid, contains Salicine, but reaction not quite so marked as before.
11			
12	88	20	
1 p.m.			4 p.m. Urine, passed 10 minutes since, is neutral; contains dense white pp. of phosphates; slight purple colour produced with 2 drops of L. F. P., showing a trace of Salicine still present.
2			
3			
4	84	24	
5			
6	84	22	
7			
8			
9			
10	84	16	12 noon. Dinner—mutton, potatoes, greens. A poor dinner.
11			4 p.m. Tea—bread and butter, one egg, and mug of milk. A good meal.
12			

The chart (Chart II.) which we have given will show that on the first day the temperature rose between 9 a.m. and 1 p.m. $\frac{9}{10}^{\circ}$ Fah. and then slowly fell; the diurnal variation apparently beginning about 6 p.m. and amounting to 2.9° Fah. Next day, also without salicine, the course of the temperature was very singular. It remained pretty stationary from 9 a.m. till 1 p.m. and then fell 1° , remaining about this point till 9 a.m. and again fell 1.6° ; the diurnal variation amounting to 2.3° . Next day, the first on which salicine was given, the temperature fell after the first dose of 30 grains $.4^{\circ}$ in $1\frac{1}{2}$ hour, and remained depressed for about 3 hours, and then rose to its original height in spite of the continuance of the medicine. The evening fall began at 7.30 p.m. and the diurnal variation amounted to 1.9° Fah. The only effect, therefore, of the salicine was a very slight and temporary depression of the temperature, not maintained by the continuance of

the medicine, and the diurnal fall was not quite so great as on the two previous days, though within the limits of variation of health.

Next day when 3 drachms of salicine in divided doses was given the temperature was not even temporarily depressed; in fact it rose $\cdot 6^{\circ}$ between 9 a.m. and 1 p.m., and then slowly fell $\cdot 3^{\circ}$ till 3.30 p.m. The evening fall began between 7 p.m. and 8 p.m., and the diurnal variation amounted to $1\cdot 5^{\circ}$.

Next day, with very marked symptoms, though without salicine, the temperature ran the same course, rising gradually from 9 a.m. till 1 p.m., and after 4 p.m., slowly falling till 12 p.m.; the daily variation amounting to only $0\cdot 9^{\circ}$. On these two days the only apparent effect therefore of salicine was to lessen the diurnal range, with a very slight increase in the maximum temperature of the day; and, strange to say, these effects were marked most on the day following the large doses of salicine, not on the day the large doses of salicine were taken, but on the following day.

Next day, taking the temperature as usual, it remained pretty stationary, varying only $\cdot 2^{\circ}$ from 9 a.m. till 6 p.m. and then fell, the diurnal variation amounting to $1\cdot 8^{\circ}$.

On the two days following the temperature returned to the course it observed on the first non-medicine day, slightly rising from 9 a.m. till 1 p.m., the rise amounting to $0\cdot 5^{\circ}$ Fah., and then the diurnal fall began respectively at 7 p.m. and 6 p.m. and amounted to $2\cdot 2^{\circ}$ and $1\cdot 7^{\circ}$.

We now summarize our observations in the following table:

Date.	Medicine given.	Amount.	Maximum temperature of the day.	Amount of diurnal variation.
Sep. 19	None		99.1	2.9
„ 20	None		98.9	2.3
„ 21	Salicine	3 iii	98.9	1.9
„ 22	Salicine	3 j	99.3	1.5
„ 23	None		99.5	0.9
„ 24	None		99.4	1.8
„ 25	None		99.5	2.2
„ 26	None		99.5	1.7

We may remark that in these observations, taken in the rectum, very little and generally no rise of temperature occurred after food—a circumstance strongly favouring a previous suggestion, that the rise after food, in cases where the temperature is taken under the tongue, is due to the hot food heating the mouth by direct contact.

This table, coupled with preceding observations, shows that even very large doses, as large as can be safely given, depress the temperature very little, and only after the first few doses, and subsequently, instead of lowering the temperature, the drug produces slight fever; thus it slightly raised the temperature, though not above the limits of health, but delayed the onset of the evening fall, and lessened the amount of diurnal variation, thus giving evidence of the febrile movement. This slight fever may, we think, be due to catarrh of the stomach, caused by the medicine, which, in so many instances excites vomiting.

In this case the pulse and respirations were greatly affected, both being considerably quickened. As was the case with the temperature, so with the pulse and respiration, the effects of the medicine were most marked the day after the discontinuance of the drug. Thus the full effects as regards the pulse and respirations and other symptoms culminated about 1 p.m. on the day following the withdrawal of the drug, the pulse at that time being 140 and the breathing 40. On the following day, that is, two days after the administration had ceased, the pulse and respirations had greatly fallen, but were still quick and next day they became normal. The pulse when frequent was very compressible, but improved in quality as it diminished in frequency.

The drug's influence on the pulse and respiration is shown in the following table:—

Date.	Medicine.	Amount of Medicine.	Maximum and minimum pulse of the day.	Maximum and minimum respiration of the day.
Sep. 19	None		66 to 84	18 to 28
„ 20	None		68 to 72	20 to 24
„ 21	Salicine	3 iii	68 to 78	24 to 28
„ 22	Salicine	3 j	88 to 116	24 to 30
„ 23	None		112 to 140	22 to 40
„ 24	None		82 to 108	18 to 28
„ 25	None		72 to 100	18 to 26
„ 26	None		76 to 88	16 to 24

We now give a resumé of his symptoms. Nothing was noticed till noon of the second salicine day until the boy had taken in all 3v. of the medicine. Between one and two we noticed that his face was flushed and he looked dull, and that there was some tremor when his hand was held out. In the evening the tremors were more marked. At 5 a.m. the following day he twice vomited. On this day though he had discontinued the medicine since five o'clock the previous evening, his symptoms were very marked and for the most part of the same characters as in the other lad,—namely dulness, so that he did not seem very well to understand questions; deafness; tingling in the right ear; slight tremor of the lips on speaking and thick husky voice; breathing rather laboured; trembling of hands when held out; slight spasmodic movements of the upper limbs; slight jerks of the lower limbs when they are raised from the bed; grasping power weaker than before; much irritability of the muscles on percussion; but strange to say he never complained of headache nor buzzing. These symptoms were at their height at midday, and were so marked and the pulse and respirations so quick, that we must confess we felt a little relief when the toxic symptoms, which became far more marked than we had expected, abated, not that at any time the boy was dangerously ill, but as the symptoms progressed, after discontinuing the medicine, we did not know how long and to what degree they might increase.

Next day, that is, forty-one hours after the last dose of medicine, he was still deaf, though less so, and was dull and unless spoken to lay with his eyes half closed, and very often fell asleep. Muscular irritability had diminished and the hands and arms trembled when held out: the pulse was still compressible. Even sixty-five hours after the last dose he was still dull, rather deaf, and there was slight tremor of the hands and irritability of percussed muscles.

Next day he had quite recovered. We tested the urine frequently for salicine and found some even 95 hours after the last dose.

In our third series of observations on a lad aged ten, and weighing 64 lbs., we experimented in a somewhat different way. We took the temperature under the tongue every three hours. For three days we administered no medicine; on the following twenty-six days we gave salicine in increasing doses, at first in 20 grain (80 grains daily), and latterly in 30 gr. doses several times daily, till he was taking in divided doses 180 grains daily. The boy got up and spent the day about the ward.

We put our observations into the following table :

	Medicine.	Maximum temperature of day.	Average temperature of day till 9 p.m.	Average till 12.	Diurnal variation to 9 p.m.	Diurnal variation to 12 p.m.	Highest pulse of the day.
1st day	None	99.2	98.66		1.1		84
2	"	99	98.64		1.2		80
3	"	99	98.6		1.2		84
7th day	80 grs.	99.1	98.7		1.1	1.9	88
8	"	99.2	98.8		1.4		96
9	"	99.2	98.7	98.4	1.4	2.2	92
10	"	98.8	98.3	98.12	1.0	1.6	88
11	120 grs.	99.4	98.8	98.5	1.3	1.8	92
12	"	99.4	98.86	98.81	1.3	1.8	96
13	"	99.3	98.96	98.78	0.9	1.4	100
14	100 grs.	99.2	98.6	98.5	1.0	1.4	96
15	120 grs.	99.2	98.62	98.60	1.0	1.3	
16	"	99.3	98.75	98.62	1.2	1.4	96
17	"	99.4	98.48	98.32	1.9	2.2	100
18	"	98.8	98.22	98.05	1.4	1.6	92
19	"	99.3	98.66	98.51	1.3	1.5	88
20	100 grs.	99.2	98.7	98.5	1.1	1.7	
21	150 grs.	99.3	99.06	98.78	1.1	1.9	88
22	"	99.3	98.81	98.67	0.6	1.5	92
23	"	99.6	98.94	98.68	1.5	2.2	96
24	"	99.4	98.88	98.63	1.9	2.0	
25	175 grs.	99.2	98.68	98.41	1.5	2.2	96
26	150 grs.	99.2	98.9	98.73	1.2	1.8	100
27	180 grs.	99.3	98.91	98.71	0.9	1.8	96
28	"	99.5	99.05	98.82	1.1	2.0	96 [bath
29	"	100.2	99.36	99.1	2.1	2.7	Had hot air
30	"	99.5	99.11	98.91	0.7	1.8	100
31	30 grs.	99.4					
32	None	99.7	98.84	98.60	1.7	2.3	100

The preceding table (and charts which we think it unnecessary to publish) shows that these large doses of salicine had no appreciable effect on the temperature. It is true that on one day the temperature rose to 100°; but that occurred during the use of the hot air bath, employed to produce sweating, that we might test the reaction of the sweat; on the other hand the pulse was a little quickened. On the fifth day of taking salicine he complained of slight deafness, and on the tenth day it is noted that the deafness had a little increased, but two days afterwards it had disappeared. Beyond the influence on the pulse and hearing, the medicine produced no apparent effects, the boy eating well, sleeping well, and indeed appearing in all respects quite well.

CHART I

TEMPERATURE UNDER TONGUE

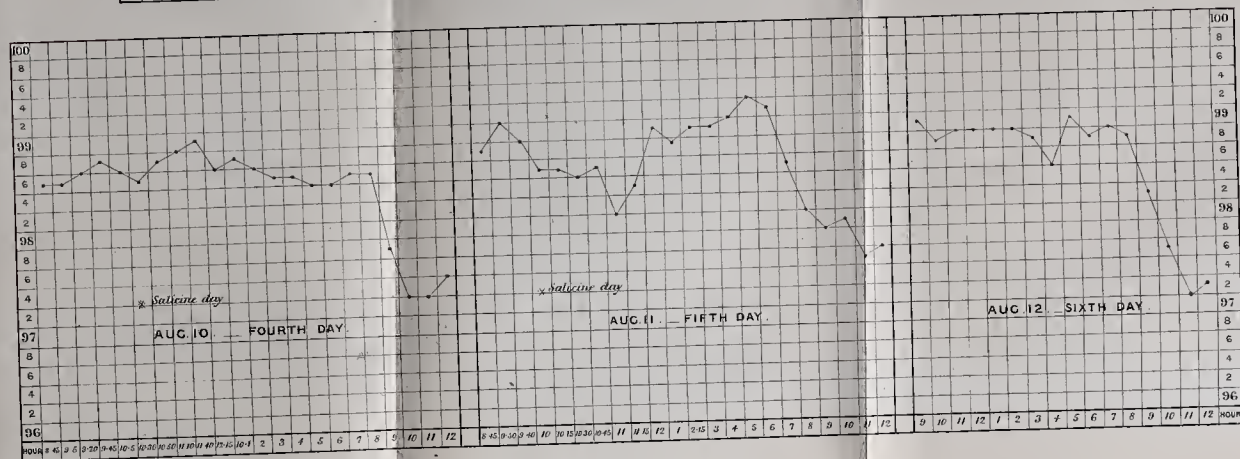
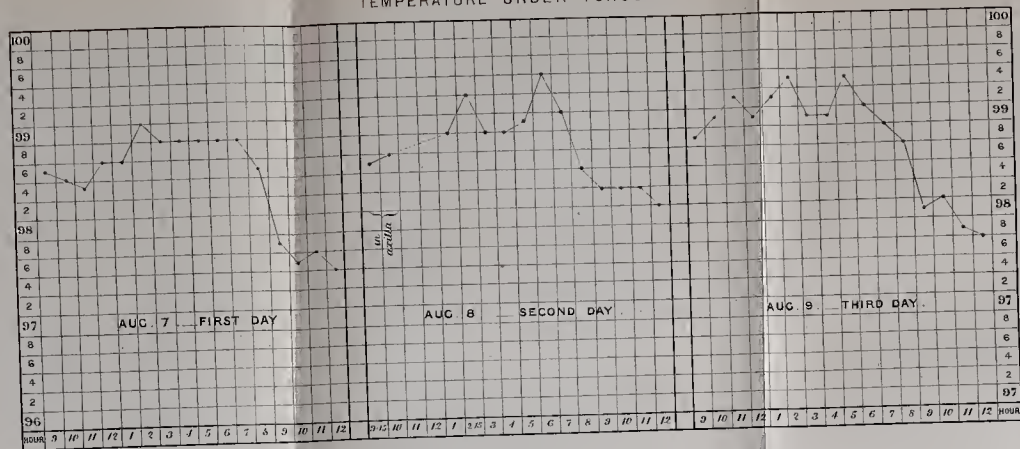
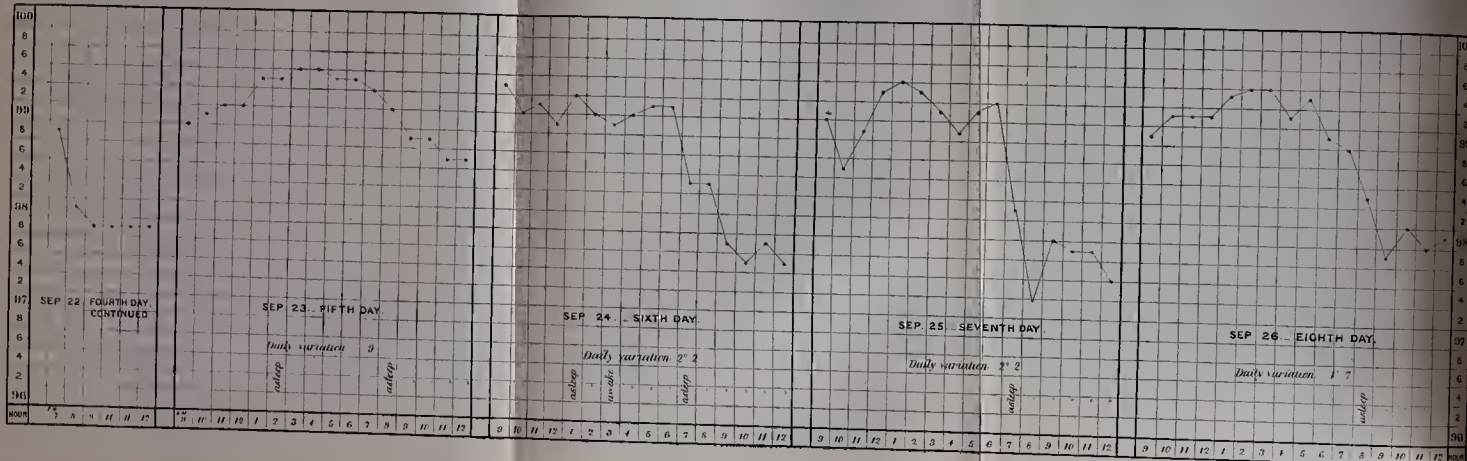
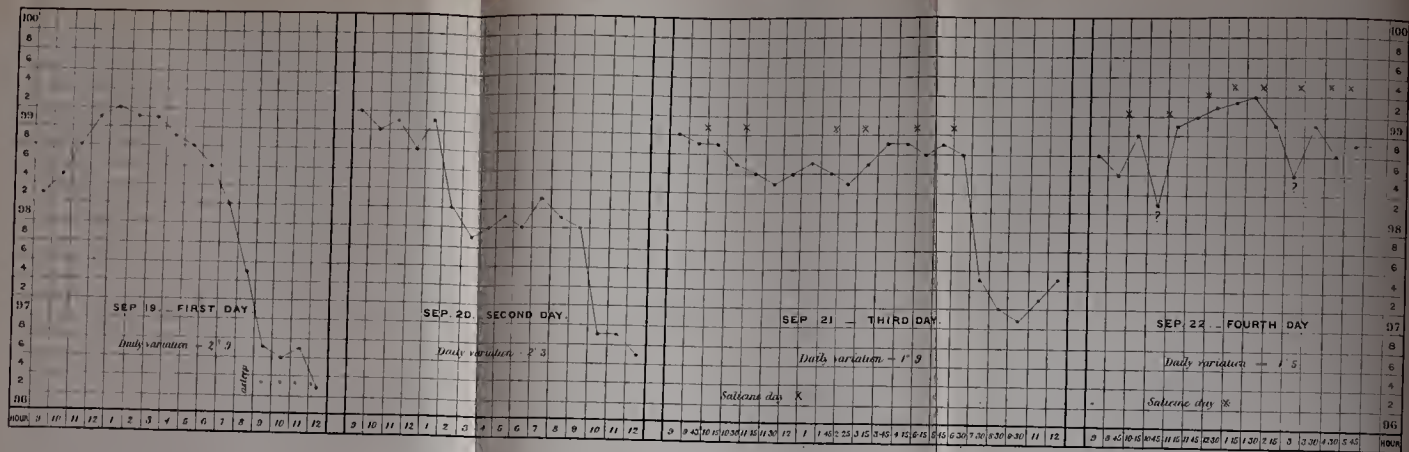


CHART II. TEMPERATURE IN RECTUM

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CONCERNING THE ACTION OF CHLORIDE OF POTASSIUM ON THE NERVOUS SYSTEM OF FROGS. By SYDNEY RINGER, M.D., *Professor of Therapeutics at University College*; and WILLIAM MURRELL, M.R.C.P., *Medical Registrar to the Westminster Hospital*.

It is well known that arrest of circulation powerfully affects the nervous system of frogs, chiefly through depression of the spinal cord. The phenomena occur in a rather peculiar order. A few minutes after the arrest of the circulation, both reflex and voluntary power become impaired; the loss of reflex action increases much more rapidly than the loss of voluntary power, so that in a short time there is complete loss of reflex action, whilst the animal still retains so much voluntary power that it can jump vigorously. At this time sensation is greatly weakened, or even destroyed—pinching the toes exciting no voluntary movement. The loss of reflex action we attribute in part to the loss of sensation, the impressions not being conducted either to the cord or brain.

It thus appears that the first effect of arrest of circulation is diminution of sensation, with slight loss of voluntary power, the impairment of sensation rapidly increasing and becoming complete, whilst the animal still has considerable voluntary power, and can hop and crawl. At this time the animal lies flat on the table, the legs being retained in any position they are placed, except when the animal voluntarily moves. Whilst sensation diminishes in two and a half minutes and is lost in about five, voluntary power, which begins to grow weak in about four minutes, is lost in about forty-nine minutes.

As many drugs which paralyse the nervous system of frogs also powerfully depress or even arrest the heart's action, we thought it possible that they might expend their force not immediately on the nervous system, but by arresting the circulation.

Thus all potash salts produce paralysis, and they also arrest the heart's action. We therefore commenced an investigation

to ascertain if potash salts paralyse through their effect on the heart, or by their direct action on the nervous tissues, or by both means.

We employed a solution of chloride of potassium, containing one part of the salt to six of water. With the chloride of potassium we poisoned frogs, and carefully watched if the symptoms occurred in the same order as after simple arrest of the circulation by ligature of the aorta. We noted likewise whether the paralysis came on sooner than from arrest of the circulation, and when the paralysis was complete we examined the web with the microscope to ascertain if the circulation was stopped, and then we opened the thorax to see if the heart's action was arrested.

We soon encountered some difficulties. Thus we found very different effects from the same dose. Following the example of other observers, and giving the salt by the mouth, we found much difficulty in administering it, and at first some escaped and ran over the animal. It then occurred to us that this difference in the effect might be due to the topical action of the drug, so we tried the effect of the application of the solution to one hind leg in two ways. In one case we merely brushed the limb with the solution; in another we wrapped the limb for some minutes in blotting paper steeped in the solution, taking care that the fluid did not come in contact with any other part of the body. We found that the local application, especially that with soaked blotting paper, completely abolished sensation, the animal remaining quiescent, manifesting neither reflex action nor pain under sharp pinching of the limb, though voluntary power remained quite unaffected, even in the poisoned limb, the animal using both hind limbs equally. The salt must therefore have paralysed the terminations of the afferent nerves. Some minutes after we noticed in the poisoned anæsthetic limb a loss of voluntary power, which progressively increased, till in a few minutes it became complete. At this time the salt must have soaked through the skin, and affected either the motor nerves or the muscles, or both. Shortly before the poisoned leg became completely paralysed, slight general paralysis set in, and this gradually became complete. This general paralysis must be due to general poisoning through absorption by the blood-vessels.

The affection of the motor nerves or muscles proves that the chloride has no especial affinity for the afferent nerves, but their terminations being chiefly in the skin, they become earlier affected than the more deeply seated parts. The animal seemed quite well again after some hours, all the paralysis having disappeared, proving that the chloride does not destroy the structures, but only suspends their function.

It is evident, therefore, that in order to ascertain the effect of the drug on the system, we must administer it by the mouth, taking care that none escapes over the skin.

In order to be sure that none escaped from the mouth, we passed a tube down the œsophagus, a plan not without difficulties, and then poured the solution into the stomach.

Having thus cleared the way for our investigations, we next proceeded to ascertain the order in which the symptoms set in after poisoning with chloride of potassium. With one exception we found the symptoms occurred in the same order as after arrest of the circulation. Thus, loss of sensation and reflex action set in sooner than loss of voluntary power, and indeed became complete, whilst a very considerable amount of voluntary power remained, so that an animal unable to feel, and unsusceptible to the excitation of any reflex action, could hop well and crawl.

The single difference just referred to, between the effect of arrest of circulation and poisoning by chloride of potassium, is that after arrest of the circulation reflex action of the eyelids, that is, closing of the eyelids on touching the ball of the eye, continues for some time after complete loss of reflex and voluntary action; whilst after poisoning by chloride of potassium, this reflex action disappears early, apparently as early as reflex action in other parts of the body.

This order of the oncoming of the phenomena favours the idea that chloride of potassium acts by arresting the heart's action.

We now proceeded to compare the relative time that chloride of potassium and arrest of the circulation respectively take to manifest their effects, and throw our results, the averages of twelve experiments, into the following table:—

Effects of Chloride of Potassium administered by the Stomach.

Reflex action and sensation destroyed.	Voluntary power impaired.	Voluntary power destroyed.
4·8 minutes.	2·7 minutes.	33·1 minutes.

Arrest of Circulation.

5·3 minntes.	3·8 minutes.	49· minutes.
--------------	--------------	--------------

At first sight it might seem that this table shows also that chloride of potassium produces its paralysing effects by arresting the heart's action; for it may be said that although there is a difference in the figures, and chloride of potassium paralyses quicker than arrest of the circulation, yet the difference is not very great. But it must be recollected that the chloride paralyses the heart but gradually, and that the arrest of the circulation therefore takes place gradually, hence the general paralysis should occur some time later instead of sooner than after simple arrest of circulation, and we conclude, therefore, that chloride of potassium does not produce its paralysing effect exclusively through its action on the heart, a conclusion confirmed by the fact that the loss of voluntary power becomes very marked much sooner after chloride of potassium than after arrest of the circulation. Moreover, we find that with chloride of potassium the paralysis is sometimes complete, whilst the circulation in the web is pretty active, and whilst the heart still continues to beat, though languidly.

We conclude, therefore, that the paralysis from the drug is not exclusively due to its action on the heart,—not exclusively, for it is obvious that an agent which greatly weakens the heart must in some degree weaken the nervous system. The production of local loss of sensation, and then local motor paralysis, by the application of the chloride to the frog's leg, clearly shows that it acts directly on the nervous system, and if the topical application of the salt can produce these effects, so it can *a fortiori* when conducted to the nervous structures by means of the blood through the blood-vessels.

THE INFLUENCE ON THE AFFERENT NERVES OF
THE FROG'S LEG FROM THE LOCAL APPLICATION
OF THE CHLORIDES, BROMIDES, AND IODIDES
OF POTASSIUM, AMMONIUM, AND SODIUM. By
SYDNEY RINGER, M.D., *Professor of Therapeutics at Uni-
versity College*; and E. A. MORSHEAD, M.R.C.S., L.R.C.P.,
Physicians' Assistant at University College Hospital.

IN the previous paper we described the effect of the local application of a solution of chloride of potassium to the leg of a frog. We have shown that it first induces complete paralysis of the afferent nerves of the immersed leg; next, motor paralysis of the leg, with some general weakness; and lastly, complete general paralysis, and that from all these effects the animal in a few hours often recovers. In the present paper, in following up this subject, we have compared the effect of potassium with the effects induced by the corresponding ammonium and sodium salts, and we have likewise compared the action of various potassium salts with one another.

Both Guttman and Podocæpow find that the injection of potash salts produces in frogs complete general paralysis, and arrest of the heart in diastole. Guttman found, too, that potash salts are far more poisonous than soda salts—that potash salts are equally poisonous and equally fatal in the same space of time, if given in the same way, and that therefore the acid of the salt plays no part in the fatal result. Guttman's experiments lead him to conclude that potash salts poison by their action on the spinal cord, the posterior part being affected before the anterior, and that the muscles and nerves are unaffected, whilst Podocæpow attributes the paralysis to the action of the potash on the muscles. Our experiments, though not designed to test the effect on the cord, yet certainly show that potash salts affect the terminations of the afferent nerves, and the motor nerves or muscles; for, as we have seen, under the external application of the salt, impressions are not conducted to the cord or brain, the animal still retaining voluntary power, and after a time the poisoned leg becomes paralysed, a phenomenon which must be due either to the action of the salt on the motor nerve or muscles, or on both.

We enclosed the frog in a wet cloth, and passed the left leg

through a hole in the cloth, and immersed this member in the solution, in one set of experiments, for thirty seconds, in another, for two minutes. Then we wiped the leg free from any of the solution, thus taking care that the solution came in contact only with the left leg.

The effect on sensation we tested every few minutes, pinching the toes, and by extending by one toe, first the poisoned and then the opposite leg with a pair of forceps. By this means we could detect even slight paralysis, and when the poisoned leg could be extended from the body, and the toes, foot, or leg pinched without causing retraction of the leg on the trunk, or exciting voluntary movement, though the voluntary power of the leg remained intact, we concluded that the terminations of the afferent nerves were paralysed, and that no impressions were conveyed to the cord or brain. When the afferent nerves were only blunted, their functions being only in abeyance, we found that the immersed leg could be much more easily extended (there being much less resistance), and would then remain extended, whilst a harder pinch was necessary to excite voluntary movement than was required in the other leg.

We always used a solution containing one part of chloride of potassium in six of water, being the strength employed by Podocaepow. In our preliminary investigations we found that by immersion of the leg in the same solution for the same space of time we obtained different results; thus, whilst in some frogs the effect was limited to paralysis of the afferent nerves, in some the immersed leg became paralysed, and in others the whole animal became paralysed, these varying results depending on the amount of the solution absorbed by different frogs. To prevent absorption as far as possible we kept our frogs in water, to maintain the repletion of the vascular system, as we required only to elicit the local effects on the afferent nerves, and then we found our results were more uniform, and usually accompanied with but little general or local paralysis of motion.

We first tested the comparative effects of chloride of potassium, chloride of ammonium, and chloride of sodium, performing two sets of experiments, in the first immersing the leg for thirty seconds, in the second, for two minutes.

We put our results in the following table:—

Chloride of Potassium.—*Solution 1 in 6.*—*Leg Immersed Thirty Seconds.*

Date.	Immersed Leg.			Lasted.	
	Loss of Sensation Begun.	Amount of Loss.	At Height.		
March 19	Immediately.	Complete.	...	34 min.	Slight general paralysis, beginning in 4 min., at height in 8 min. Animal completely recovered.
"	"	"	...	126 "	Decided general weakness, beginning in 2 min. Animal recovered.
"	"	"	...	50 "	Slight general weakness, " 5 "
"	"	"	...	30 "	" " " 7 "
"	"	"	1/2 min.	63 "	No general weakness, " "
"	"	"	...	56 "	Decided general weakness, " 6 "
		Average, .	.	59.8	
		<i>Chloride of Ammonium.</i>			
"	"	Complete.	5 min.	15 min.	Slight general weakness. Animal recovered.
"	"	"	3 "	28 "	Doubtful general weakness. " "
"	"	Incomplete.	Immediately.	5 "	Slight general weakness. " "
"	"	Complete.	2 min.	22 "	" " " "
"	"	"	9 "	30 "	" " " "
"	"	"	2 "	35 "	" " " "
"	"	Average, .	.	22.5	
		<i>Chloride of Sodium.</i>			
"	"	None.*	...	...	* We thought at first there was slight loss of sensation in the immersed leg; but the difference was insignificant, and persisted throughout our observation, the difference probably being natural.
"	"	"	...	...	
"	"	"	...	...	
"	"	"	...	...	
"	"	"	...	...	
"	"	"	...	...	

INFLUENCE OF SALTS ON AFFERENT NERVES.

Leg Immersed for Two Minutes.—Chloride of Potassium.

Immersed Leg.					General Paralysis.				
Date.	Loss of Sensation begun.	Amount of Loss.	At Height.	Lasted.	Begun to Improve.	Begun.	Amount.	At Height.	Begun to Improve.
March 23	Immediate.	Complete.	Immediate.	2 h. 35 min.	...	4 min.	Slight.	4 min.	1 h. 17 min.
" "	"	"	"	3 hours.	...	Immediate.	Almost complete.	1 h. 45 min.	2 h. 30 min.
" "	"	"	"	1 h. 37 min.	...	3 min.	Very slight.	23 min.	37 min.
" 42	"	"	"	40 min.	...	2 "	"	...	...
" "	"	"	"	65 "	...	2 "	Slight.	5 "	...
" "	"	"	"	2 h. 44 min.	...	Immediate.	"	8 "	...
Average, . . .					...				

General weakness no greater, with one exception that followed after thirty seconds' immersion.

Chloride of Ammonium.

March 26	Immediate.	Complete.	Immediate.	61 min.	...	...	No general weakness.	...	...
" "	"	"	"	58 "	...	...	"	...	...
" "	"	"	"	37 "	...	...	"	...	...
" 27	"	"	"	35 "	...	...	"	...	...
" "	"	"	"	22 "	...	...	"	...	...
" "	"	"	"	36 "	...	...	"	...	...
Average, . . .					...				

41.5 min.

Chloride of Sodium.

March 29	Immediate.	Distinct.	Immediate.	18 min.	...	...	None.	...	...
" "	"	Complete.	"	21 "	...	Immediate.	Slight.	Immediate.	2 min.
" "	"	No effect at all.	"	"	...	"	None.	"	...
" 27	Immediate.	Complete.	Immediate.	24 "	...	"	Slight.	"	3 "
" "	"	"	"	34 "	...	"	"	"	2 "
" "	"	Slight.	"	3 "	...	...	None.	"	...
Average, . . .					...				2.3

16.6

The preceding tables lead to the conclusion that the action of these three salts differs only in degree, chloride of potassium having the greatest effect, next chloride of ammonium, and last, chloride of sodium. In the experiments where the immersion lasted only thirty seconds, it is true that chloride of sodium produced no effect, but the two minutes' immersion produced a very decided, though very transient, effect.

In the following tables we now give the average results obtained from the preceding tables:—

Effect of Thirty Seconds' Immersion.

	Loss of sensation lasted.
Chloride of potassium, ...	59·8 min.
Chloride of ammonium, ...	22·5 „
Chloride of sodium, ...	No effect.

Effect of Two Minutes' Immersion.

Chloride of potassium, ...	117·0 min.
Chloride of ammonium, ...	41·5 „
Chloride of sodium, ...	16·6 „

It will be noticed that in the case of chloride of potassium and chloride of ammonium two minutes' immersion caused paralysis lasting just double the time that followed thirty seconds' immersion. In all these experiments some of the salt appears to have been absorbed into the general circulation, for in most of the experiments we produced general weakness in addition to loss of sensation in the immersed leg. This general weakness occurred in all the potash and ammonium frogs after thirty seconds' immersion, the effect being greater from chloride of potassium than from chloride of ammonium. The frogs treated with chloride of sodium were unaffected. After two minutes' immersion, strange to say, the effects were different. Thus chloride of potassium caused no greater general paralysis than after only thirty seconds' immersion, and the chloride of ammonium produced no general weakness, whilst in three of the chloride of sodium frogs there occurred general weakness, though of very short duration, suddenly disappearing in about two to three minutes, the animal almost at once regaining full voluntary power; the complete paralysis of the immersed leg passing

off at the same time and equally suddenly, though some paralysis of sensation remained for some minutes longer. The effect on sensation was always manifested immediately after the process of immersion, and with one exception, in the thirty-second series, after chloride of potassium the effect on sensation was at its height immediately after. After chloride of ammonium the greatest effect did not occur, with one exception, so soon, being at its height on an average in 3·5 minutes after immersion. In the two minutes' series of observations, in every case, with chloride of potassium and chloride of ammonium respectively, the effect was at its height immediately after immersion, and the paralysis was complete; whilst with chloride of sodium the loss of sensation was complete in three instances, distinct in one, slight in one, and absent in one, and, as in the case of the potassium and ammonium salts, the loss was at its height immediately on removing the leg from the solution.

An inspection of the subjoined table will, we think, justify our conclusion that the difference in the local action manifested by each of these three salts is one only of degree.

Potash Solution for Thirty Seconds.

Date.	Loss of Sensation in Immersed Leg.		Paralysis of Immersed Leg.		
	Degree.	Begun to Im- prove.	Degree.	Begun to Im- prove.	Recov- ered.
		Min.		Min.	Min.
Mar. 8	Complete general paralysis.		None.	...	...
„ 19	Complete.	27	„	...	...
„ 19	„	65	Complete.	14	...
„ 19	„	26	Distinct.	...	...
„ 20	„	18	None.	...	..
„ 20	„	32	„	...	...
„ 20	„	26	„	...	...
		32·3			

Chloride of Ammonium—Thirty Seconds.

Mar. 21	Complete.	9	None.	...	...
„ 21	„	20	Slight.	...	4
„ 21	Nearly „	3	None.	...	...
„ 21	Complete.	5	„	...	...
„ 21	„	12	„	...	...
„ 21	„	11	„	...	...
		10			

Chloride of Potassium—Two Minutes' Immersion.

Date.	Loss of Sensation in Immersed Leg.		Paralysis of Immersed Leg.		
	Degree.	Begun to Im- prove.	Degree.	Begun to Im- prove.	Recov- ered.
Mar. 23	Complete.	Min. 90	None.	Min. ...	Min. ...
" 23	"	174	Slight.	144	...
" 23	"	82	None.	...	...
" 24	"	20	"	...	...
" 24	"	25	"	...	...
" 24	"	99	Marked.	54	...
		81.6			

Chloride of Ammonium—Two Minutes' Immersion.

Mar. 26	Complete.	11	...	None.	...
" 26	"	12	...	"	...
" 26	"	14	...	"	...
" 27	"	25	...	"	...
" 27	"	9	...	"	...
" 27	"	10	...	"	...
		13.5			

Chloride of Sodium—Two Minutes' Immersion.

Mar. 27	Complete.	8	Complete.	few sec	3
" 27	Slight.	3	None.	...	...
" 29	Distinct.	5	"	...	...
" 29	Complete.	2	Complete.	30 sec.	2
" 29	None.	...	None.	...	...
" 29	Complete.	3	Complete.	1 min.	3
		3.5			

The difference in the degree of sensation in the immersed leg is shown in another way; thus sensation began to return much sooner after the chloride of ammonium, and still sooner after the chloride of sodium, than would have been expected from the time the loss of sensation continued. The following evidence, extracted from the preceding tables, exemplifies this:—

	Immersion.	Loss of Sensation Lasted.	Begun to Improve.
		Minutes.	Minutes.
Chloride of Potassium, . .	30 seconds.	59.8	32.3
" Ammonium, . .	"	22.5	10
" Potassium, . .	2 minutes.	117	81.6
" Ammonium, . .	"	41	13.5
" Sodium, . .	"	16.6	3.5

Thus though chloride of sodium paralysed sensation in the immersed leg, the paralysis lasted a far shorter time than that following potash, potash paralysing about seven times longer than sodium. But the recovery from complete sodium paralysis is much quicker than that from potash; thus after sodium, sensation began to return nine times earlier than after potash. Though after immersion in the chloride of sodium for two minutes there was complete sensory paralysis, yet sensation very promptly began to return, though a very slight diminution of it remained for some time afterwards.

Strange to say, the chloride of sodium produced a far greater degree of motor paralysis than the chloride of potassium or ammonium. Thus in the two minutes' experiments chloride of potassium caused slight loss of power in 1 frog, marked loss of power in 1 frog, no loss of power in 4 frogs.

In six experiments no loss of power occurred in the leg immersed in solution of chloride of ammonium; whilst after chloride of sodium the loss of power was complete in 3 frogs, and there was no loss in 3.

But whilst the degree of motor paralysis in the immersed leg was far greater with chloride of sodium than with either of the other two salts, the paralysis was much more enduring after potash. Thus after immersion in the potash solution the loss of power only begun to be restored in 144 and 54 minutes respectively; whilst after chloride of sodium immersion improvement began in a few seconds, and in 3, 2, and 3 minutes respectively there was complete restoration.

We next performed a corresponding series of experiments with bromide of potassium, bromide of ammonium, and bromide of sodium.

We now give a summary of our conclusions with respect to the action of these salts in the following tables:—

Bromide of Potassium.—Solution 1 in 6.—Leg Immersed Thirty Seconds.

Immersed Leg.					General Paralysis.				Paralysis of Immersed Leg.		
Date.	Loss of Sensa- tion Begun.	Amount of Loss.	At Height.	Lasted.	Begun.	At Height.	Begun to Improve.	Result.	Degree.	Begun to Improve.	Recovered.
March 31	Immediately.	Slight.	Immediately.	13 min.	Very slight. None.	Very slight. None.	...	...	None.	...	
" 31	"	"	1 minute.	6 "							
" 31	"	Distinct.	Immediately.	8 "							
" 31	"	Slight.	"	18 "							
" 31	"	Very slight.	"	3 "							
" 31	"	Slight.	"	12 "							
Average, . . .					10 min.						

Bromide of Ammonium.—1 in 6.—Thirty Seconds' Immersion.

Date.	Loss of Sensation Begun.	Amount of Loss.	At Height.	Lasted.	General Paralysis.				Paralysis of Immersed Leg.		
					Begun.	At Height.	Begun to Improve.	Result.	Degree.	Begun to Improve.	Recovered.
April 2	Immediately.	Almost complete.	Immediately.	6 min.	None.		...	...	None.		...
" 2	"	Slight.	"	3½ "		"	...	...	"		...
" 2	"	Distinct.	"	7 "		"	...	...	"		...
" 2	"	"	"	10 "		"	...	...	"		...
" 2	"	Complete.	3 minutes.	9 "		"	...	...	"		...
" 2	"	Slight.	"	5 "		"	...	...	"		...
Average, . . .				6.6 min.							

Bromide of Sodium.—1 in 6.—Leg Immersed Thirty Seconds.

Date.	Loss of Sensation Begun.	Amount of Loss.	At Height.	Lasted.	General Paralysis.				Paralysis of Immersed Leg.		
					Begun.	At Height.	Begun to Improve.	Result.	Degree.	Begun to Improve.	Recovered.
April 3	Immediately.	Very slight.	3 minutes.	13 min. ¹	...	...	...	...	...	...	...
" 3	"	None.	...	5 "	...	...	...	...	...	...	...
" 3	"	Doubtful.	...	...	...	...	...	...	...	...	...
" 3	"	None.	...	...	...	...	...	...	...	...	...
" 3	"	"	...	...	...	...	...	...	...	...	...
" 3	"	Very slight.	...	2 "	...	...	...	...	...	...	...
Average, . . .				3.3 min.							

¹ The loss of sensation in the immersed leg was so slight that we found it difficult to be quite sure of the time when sensation returned. We think these figures are not worth much.

INFLUENCE OF SALTS ON AFFERENT NERVES.

Bromide of Potassium.—Solution 1 in 6.—Leg immersed Two Minutes.

Immersion Leg.				General Paralysis.				Paralysis of Immersed Leg.			
Date.	Loss of Sensation Begun.	Amount of Loss.	At Height.	Begun to Improve.	Lasted	Begun.	At Height.	Amount.	Begun to Improve.	Result.	Amount.
Apr. 4	Immed.	Complete	Immediately	hrs. min.	h. m.	min.	7 mins.	Slight.	min.	Recovd.	Slight.
" 4	"	"	"	26	67	5	Last only a few mins.	"	12	"	None.
" 4	"	"	"	26	69	5	2 hours.	"	...	"	Complete
" 4	"	"	"	1 47	2 50	24	5 mins.	Slight.	23	"	None.
" 4	"	"	"	2 7	3 53	12	2·18	Almost com.	...	"	Complete
" 4	"	"	"	2 7	2 24	...	...	None.	...	"	None.
Average,				.	135						

Bromide of Ammonium.

Apr. 5	Immed.	Complete	Immediately	9	69	...	None.	None.	...	...	None.
" 5	"	"	"	10	51	...	"	"	...	...	"
" 5	"	"	"	8	13	...	"	"	...	...	"
" 6	"	"	"	32	65	...	"	"	...	...	"
" 6	"	"	"	20	45	...	"	"	...	...	"
" 6	"	"	"	39	80	...	"	"	...	...	"
Average,				.	53·8						

Bromide of Sodium.

Apr. 7	Immed.	Complete	Immediately	...	6	Immed.	Immediately	Considerable	Few secs.	...	Complete	Immed.
" 7	"	"	"	...	5	"	"	"	2 mins.	...	"	"
" 7	"	"	"	...	7	"	"	"	1½	...	"	"
" 7	"	"	"	...	9	"	"	"	3	...	"	"
" 7	"	"	"	...	9	"	"	"	1	...	"	"
" 7	"	"	"	...	4	"	"	"	2	...	"	"
Average,				.	6·6				1·6			1·6

The results from this series of experiments with bromides are very similar to those obtained from chlorides. Thus we find that the difference between bromide of potassium, bromide of ammonium, and bromide of sodium, is for the most part one of degree, for each produced loss of sensation in the immersed leg; and as in the case of the corresponding chlorides, the potassium is the most powerful paralysing; ammonium salt comes next, and the sodium is the weakest, inducing, in thirty seconds, very little diminution of sensation, but a more decided loss after two minutes' immersion.

Whilst in each instance the effects on the sensation of the immersed leg, after thirty seconds, differs considerably from those occurring in the chloride series, yet after two minutes' immersion the results are very similar in both series of salts.

In the following tables we give the average results after immersion with the two series of salts:—

Time Sensation Remained Impaired in the Leg after Thirty Seconds' Immersion.

	Bromide.	Chloride.
Potassium, . . .	10 min.	59·8 min.
Ammonium, . . .	6·6 „	22·5 „
Sodium, . . .	3·3 „	No effect.

After Two Minutes' Immersion.

Potassium, . . .	135 min.	117 min.
Ammonium, . . .	53 „	41 „
Sodium, . . .	6·6 „	16·6 „

In this table we have stated that the bromide of sodium immersion, after thirty minutes, produced paralysis of the leg, lasting on an average 3·3 minutes; but we are bound to state that in three of the six experiments there was no paralysis, in two it was doubtful, and in one it was very slight; indeed, so slight that we could not ascertain clearly how long it lasted, and hence this division of the table is of little value.

In the two minutes' immersion experiments the bromide of potassium produced in five of the six frogs general loss of power, slight in three, and almost complete in two, and in these it persisted over two hours.

With bromide of sodium we also obtained results identical with those occurring after the two minutes' immersion in the chloride of sodium solution; thus on withdrawing the immersed leg, and laying the animal on its back, it remained in this position, and superadded to this general weakness, there was complete paralysis of the immersed leg. This general weakness and complete paralysis of the immersed leg entirely disappeared on an average of 1·6 minutes, the animal hopping as vigorously as ever, and using both hind legs equally well. These effects occurred only with three of the chloride of sodium frogs, but in all six of the bromide of sodium.

We next proceeded to test in the same way as heretofore the effect of iodide of potassium, ammonium, and sodium, and we give the results in the accompanying tables:—

Iodide of Potassium.—Leg Immersed Two Minutes.

Date.	Immersed Leg.				General Paralysis.				Paralysis of Immersed Leg.			
	Loss of Sensation Begun.	Amount of Loss.	At Height.	Begun to Improve.	Lasted.	Begun.	At Height.	Amount.	Begun to Improve.	Re-covered.	Amount.	Begun to Improve.
Apr. 9	Immed.	Complete.	Immediately	hrs. min. 2·45	hrs. min. 3·22	1·30	1·30	Marked.	min. 2·30	min. 3·22	Decided.	min. ...
" 9	"	"	"	2·18	4	Died in an hour and half.	No loss.	None.	...	...	Complete	...
" 9	"	"	"	...	...	Died in two hours.	Died in two hours.	None.	...	...	"	...
" 10	"	"	"	4·10	4·40	Immed.	Immed.	Slight.	...	16	Complete	...
" 10	"	"	"	1·10	2·5	3 min.	...	Doubtful	...	20	"	...
" 10	"	"	"	1 10	1·25	Immed.	Immed.	Decided.	...	...	"	...
" 16	"	"	"	3½	4	"	"	Slight.	...	...	"	...
" 16	"	"	"								"	
Average,				.	190							

Iodide of Ammonium.

Apr. 11	Immed.	Immediately	Immediately	6	46	None.	None.	...	None.	...	...	...
" 11	"	"	"	8	38	"	"	...	"	...	...	...
" 11	"	"	"	3	19	"	"	...	"	...	...	...
" 12	"	"	"	1·8	2·27	Decided.	Decided.	...	...	...	Complete	...
" 12	"	"	"	62	79	Decided but slight.	Decided but slight.	...	...	...	...	...
" 12	"	"	"	11	29	None.	None.	Complete	...	...	...	...
"	"	"	"		59·6			...	None.	...	...	...
Average,				.								

Iodide of Sodium.

Apr. 13	Immed.	Complete.	Few secs.	3	7	...	None.	...	None.	...	...	...
" 13	"	Diminished.	"	...	4	...	"	...	"	...	...	...
" 13	"	Complete.	Immediately	...	4	Immed.	Immed.	Complete	...	1	Complete	...
" 13	"	"	"	1½	4½	"	"	"	...	1½	"	...
" 13	"	"	"	2	6	"	"	"	...	1½	"	...
" 13	"	"	"	...	...	"	"	"	...	...	"	...
"	"	No effect.	"	...	...	"	"	"	...	...	"	...
Average,				.	4·2							

* Died in night.

We produced far more decided local effects with iodide of potassium than with the other potassium salts. Thus with this agent in every case some motor paralysis occurred in the immersed leg, slight in two cases, decided in one, complete in three, and this paralysis or weakness lasted, on an average of three cases, 25·6 minutes. The leg, too, was more affected in other ways; thus the tissues looked rather swollen, and the leg seemed stiff.

We give the results of our observations in the following table:—

Duration of loss of sensation after two minutes' immersion—

	Chloride.	Bromide.	Iodide.
Potassium,	117 min.	135 min.	190 min.
Ammonium,	41 „	53 „	59 „
Sodium,	16 „	6 „	4 „

Iodide of sodium produces the same effects as the other soda salt—peculiar effects, quite different from those following the administration of potassium and ammonium salts. Thus in three of six experiments, on removing the animals from the solution, we found considerable, indeed almost complete, general paralysis, both voluntary and reflex, whilst in the immersed leg itself each form of paralysis was complete, the animal when laid on its back remaining in this posture. This paralysis very suddenly, in from one to two minutes, passed off; and the paralysis, too, of voluntary power in the paralysed leg disappeared at the same time, though paralysis of sensation remained a few minutes longer.

Our observations, then, lead us to the following conclusion:—That the local application of chlorides, bromides, and iodides of potassium, ammonium, and sodium paralyse the terminations of the afferent nerves; that the potash salts are far more powerful in this respect than the ammonium, and the ammonium than the sodium; the effect of the potassium salts lasting three to four times longer than the effects of the ammonium, and twenty to fifty times longer than the effects of the sodium.

Hence the effect on the afferent nerves depends chiefly on the base and not on the acid. Nevertheless, the paralysing

effect does not wholly depend on the potassium, as is the case when these salts are administered by the mouth or hypodermically; for our experiments show that, applied in the way previously described, the loss of sensation lasts longer with bromide than with the chloride, and nearly twice longer with the iodide than with the chloride of potassium. Now, if the paralysis depends entirely on the potassium, the loss of sensation should endure longest with the chloride, for this salt contains about half as much again of potassium as the bromide, and about twice as much as the iodide.

It occurred to us that this paralysing action of potash salts on the sensory nerves of frogs might perhaps elucidate the soothing effects of liquor potassæ and carbonate of potash in certain painful affections of the stomach; and like their action on the frog's leg, they might paralyse the ends of the sensory nerves, and thus allay pain. We five times performed the following experiment to test whether potassium salts would diminish or abolish sensation in mucous membranes. We soaked a piece of lint in a solution of chloride of potassium (1 in 4), and applied it to one-half of the inner surface of the lower lip, making the animal lie on the same side, so that the solution should not trickle over to the other side of the lip; and we exposed the mucous membrane to the action of the chloride for a period varying from five minutes to half an hour. In one case, perhaps, there was very slight diminution of sensation, but in the remaining four cases the potassium certainly failed to diminish sensation. We may perhaps venture to suggest that potash salts would manifest no greater effect on the mucous membrane of the mouth.

ON THE EFFECT OF THE CHLORIDES, BROMIDES, AND IODIDES OF POTASSIUM AND SODIUM ON FROGS.

By SYDNEY RINGER, M.D., *Professor of Therapeutics at University College*; and E. A. MORSHEAD, M.R.C.S., L.R.C.P., *Physicians' Assistant at University College Hospital*.

WE have already seen that chloride of potassium first paralyses sensation and destroys reflex action, in part at least by its action on the afferent nerves, whilst a considerable amount of voluntary action remains, so that an animal destitute of sensation and insusceptible of reflex action can still hop pretty vigorously. From the investigations of numerous writers it appears that bromide of potassium acts in much the same way as chloride of potassium. Thus, after some excitement, there follows "great muscular relaxation and total abolition of reflex action. Voluntary movements, however, often occur during this period, and the frog, which has been lying limp and apparently dead, will startle the observer by a sudden vigorous leap" (Wood's *Therapeutics*).

In this paper we propose to ascertain whether other potash salts produce the same effects in the same order, and we have therefore made a series of observations on chloride, bromide, and iodide of potassium. We have also made a series of observations on the corresponding sodium salts, in order to compare their effects with those of the potassium salts, chiefly with the view to ascertain whether and to what extent the effects on the nervous system of frogs following the administration of bromide of potassium are due to that salt or depend on the potash element. Guttman's careful experiments show that all potash salts produce identical effects, which are all due to the potash, uninfluenced by the acid in combination with it. In our observations the effects of chloride of potassium were so similar to the effects described as following the administration of bromide of potassium, that we were led to expect that they were due to the potash, and were in no way influenced by the bromide combined with it; and this supposition turned out to be correct.

This was our mode of procedure:—We employed a solution

containing one part of salt in six of water, and injected a portion of this into the connective tissue of the axilla, or close to that region, and then noted the effect every few minutes for the first two hours, afterwards at longer intervals.

Before describing the general effects, we may here state that in most of the experiments with the potash salts we produced certain local effects already noticed by other observers. Thus in some cases both the anterior limbs, in other instances only the limb into the axilla of which the injection was made, became immediately paralysed, often completely so.

We will first point out a condition of the frog under experiment,—a condition which comes on quickly and lasts a very brief space,—a condition which ensues on the injection of either the potassium or sodium salts. Immediately after the injection the animal for a few seconds jumped about vigorously, and then passed into a rather peculiar state, not unfrequent indeed after the injection of other substances. Thus the frog appeared to be completely paralysed in regard to both motion and sensation; for when placed on its back it made no effort to regain its natural position, when pinched it did not move, nor did pinching excite any reflex act, though in most cases the legs when extended were withdrawn on the body, but not nearly so vigorously as in a normal frog. In one minute to five minutes—generally in two—this condition passed away suddenly, simultaneously with the instant and complete restoration of voluntary power after the sodium salts; though, after the potassium salts, sensation, and probably reflex action (unless the weakness in this function was due to depression of the afferent nerves), remained weak for a few minutes longer. In some cases the animal never regained entire voluntary power, though it could hop pretty well.

To what is this transient condition due? To shock? The animal assumed the appearance of a much frightened frog, pulling its forelegs over its head. Against this supposition we may urge that in our immersion experiments, described in an earlier paper, this condition almost always followed an experiment with sodium solutions, but not, except in very few instances, was absent with potassium and ammonium solutions. Were it due to shock, we should expect that the condition in ques-

tion would certainly ensue after the more powerful potassium and ammonium solutions.

To ascertain if any of the effect, and if so, how much, is due to fright or shock, we performed the following experiments:—Under the skin of three frogs, into the connective tissue of the axilla, we injected 3, 4, and 6 minims respectively of pure water without producing any result. Still it seemed possible, though the water was inoperative, that a saline solution might produce cerebral shock, so we pithed and pegged the frog, that is, we divided the spinal cord opposite the occipito-atlantal membrane, and passed a peg of wood into the cavity of the skull, to destroy the brain, and to prevent hæmorrhage. Then when the effect of the shock had passed away, and the reflex action had returned, we administered the injection, and noted the effects every minute. In six frogs thus prepared we injected into each a potash solution, using respectively 3 to 6 minims, into the axilla in each instance, with one exception, and in that under the skin of the abdomen. In three of these we failed to produce the primary transient effect; in the other three we thought that soon after the injection the reflex action declined and then in a few minutes returned, but the loss, if any, was so slight that we do not feel by any means sure if the solution produced any effect on the spinal cord; and we must confess that we have been unable to satisfy ourselves as to the true nature of the primary passing symptoms occurring a few seconds after these saline injections.

Being unable to speak positively of the nature of the phenomena in question, we have included them in the tables giving the results of the sodium solutions. If these early phenomena are put down to shock, this will show still more strongly how widely different are the effects of potassium from those of sodium salts; for subtracting shock the direct effects of the sodium salts are nearly nil.

We shall now give a general description, first of the action of the potash and then of the sodium salts, premising that these three potash salts produced the same symptoms and in the same order, but that the effects progressed more rapidly with the chloride than with the bromide, and with the bromide than with the iodide. With these three potassium salts, after recovery from

the early condition just described, that is, on the complete or almost complete restoration of voluntary power, there was, with two exceptions, considerable, and in some instances complete, loss of sensation. Thus pinching a toe excited either no voluntary movement, or the limb responded only to firm and repeated pinching, though the animal at this time retained complete or almost complete voluntary power. Like sensation, reflex action was either much diminished or abolished. In five to ten minutes general weakness of voluntary power set in and steadily progressed, becoming at last complete. Long before this stage was reached the animal lay still, as if dead, incapable of being roused by pinching, though it would frequently hop or crawl vigorously.

The early loss of reflex power can be explained by the effect on the afferent nerves, which were certainly implicated; for pinching excited either no voluntary movement, or strong pinching was required to provoke it, though probably the cord is also paralysed. But as our object is not to ascertain the effects on the cord, we have not pursued this subject; for, indeed, this is not needed after Guttman's careful experiments, which prove that potassium salts paralyse by their action on the cord. We are, however, strongly inclined to attribute the loss of reflex action occurring before great loss of voluntary power rather to the influence on the afferent nerves than to the effect on the cord, as it is probable that were the cord paralysed as to reflex action, it would be likewise paralysed as to voluntary power. Even where sensation persisted for some time after the injection, the greater part of this sensation was immediately lost; for, as we have said, it required firm and repeated pinching to excite voluntary action. In two instances, after iodide of potassium, slight sensation was retained till nearly the complete loss of voluntary power.

We next give a general account of the action of these three sodium salts.

After the injection of a sodium salt, the early primary condition described included nearly all its effects. Thus in two to five minutes the animal begun to recover, and then in a few seconds it completely regained voluntary power, but loss of sensation continued a few minutes longer, shown by the fact

that pinching did not so readily excite voluntary movement as when the effects of the drug had passed away. Whilst this loss of sensation continued reflex action was also weak, due, we maintain, at least in part, and probably entirely, to the effect on the afferent nerves, though possibly also to the action of the salt on the cord. Some portion of the action, however, must be due to the effect on the afferent nerves, for if these are weakened in respect to the conduction of sensation to the brain, they must be also weakened in respect to the conduction of impressions to the cord if, as is generally held, the same fibres conduct impressions to both cord and brain.

We now give our results in the following tables:—

Chloride of Potassium.

Date.	Weight of Frogs.	Dose of Salt.	Relative Quantity of Weight of Animal.	Loss of Sensation Begun.	Loss of Sensation at its Height.	Amount of Loss of Sensation.	Sensation begun to Return.	Loss of Sensation Lasted.	General Weakness Begun.	At its Height.	Amount of General Weakness.	General Weakness begun to Improve.	General Weakness Lasted.
Apr. 26	29	gr.	$\frac{1}{895}$	Immed.	19 min.	Complete	...	...	9 min.	56 min.	...	...	Recovered.
26	32	$\frac{1}{2}$	$\frac{1}{986}$	"	2 "	"	...	...	7 "	27 "	...	...	Died.
26	29	$\frac{1}{4}$	$\frac{1}{395}$	"	17 "	"	...	...	7 "	27 "	...	...	Recovered.
28	16	$\frac{1}{8}$	$\frac{1}{741}$	"	13 "	"	...	...	5 "	43 "	...	...	Died.
28	15 $\frac{1}{2}$	$\frac{1}{8}$	$\frac{1}{716}$	2 $\frac{1}{2}$ min.	13 "	"	...	...	7 $\frac{1}{2}$ "	37 "	...	...	"
28	15	$\frac{3}{8}$	$\frac{1}{693}$	Immed.	46 "	"	...	...	4 "	52 "	...	...	"
Average,		.	$\frac{1}{821}$	18 min.				6.5		40.6			

Chloride of Sodium.

Apr. 26	28	$\frac{1}{864}$	Immed.	Immed.	Complete.	...	6 min.	Immed.	Immed.	...	2 min.
26	27 $\frac{1}{2}$	$\frac{1}{849}$	"	"	"	6 min.	14 "	"	"	...	6 "
26	11	$\frac{1}{509}$	"	"	"	6 "	9 "	"	"	...	...
28	16 $\frac{1}{2}$	$\frac{1}{764}$	Few secs.	Few secs.	"	4 "	18 "	No general weakness	"	...	2 "
28	27	$\frac{1}{833}$	"	"	"	6 "	10 "	Few secs.	"	...	4 "
28	17	$\frac{1}{787}$	Immed.	"	"	4 "	11 "	Immed.	"	...	1 "
Average,		$\frac{1}{767}$				5.2	11.3				2.5

Bromide of Potassium.

Date.	Weight of Frog.	Dose of Salt.	Relative quantity of Weight of Animal.	Loss of Sensation Begun.	Loss of Sensation at its Height.	Amount of Loss of Sensation.	Sensation begun to Return.	Loss of Sensation Lasted.	General Weakness Begun.	At its Height.	Amount of General Weakness.	General Weakness begun to Improve.	General Weakness Lasted.	
Apr. 17	19½	grm. ½	60.2	Immed.	Immed.	Complete.	min. ...	min. ...	Immed.	hrs. min. 28	Complete.	Died.	min. ...	28 mins. paralysis almost complete.
"	17	15	69.1	"	3 min.	"	"	"	"	1	"	"	"	At first got effects just like sodium salts.
"	18	14	72.96	4 mins.	9 "	Almost "	"	16	"	9	Considerable.	Recovered.	32	"
"	18	16	74.1	Immed.	8 "	Complete.	"	"	"	53	Complete.	Died.	"	"
"	20	18	83.3	"	37 "	"	"	"	"	75	"	"	"	"
"	20	16	74.1	"	Immed.	"	"	"	"	80	"	"	"	"
"	20	16½	76.7	"	1½ min.	"	"	"	17 min.	37	"	"	"	"
Average,	21	13	73.6	Immed.	8.3					55.5	No tetanus in any of these.			
"											Excluding No. 3 when only ⅙ gr. given.			

Bromide of Sodium

Date.	Weight of Frog.	Dose of Salt.	Relative quantity of Weight of Animal.	Loss of Sensation Begun.	Loss of Sensation at its Height.	Amount of Loss of Sensation.	Sensation begun to Return.	Loss of Sensation Lasted.	General Weakness Begun.	At its Height.	Amount of General Weakness.	General Weakness begun to Improve.	General Weakness Lasted.	
Apr. 17	14	1½	43.2	Immed.	Immed.	Complete.	4	7	Immed.	Immed.	Complete.	2½ mins.	2½	
"	17	13	60.2	"	"	"	2½	5	"	"	"	"	3½	
"	18	15½	74.6	"	"	"	3½	5	"	"	"	"	2½	
"	18	13	60.2	"	"	"	"	4	"	"	"	"	52	
"	20	19	78.6	"	"	"	2	5½	"	"	"	"	1½	
"	20	17	78.7	For ½ min.	½ min.	"	"	2½	"	"	Slight.	"		
Average,			66.7				3	4.8					2.2	

Iodide of Potassium.

Date.	Weight of Frog.	Dose of Salt.	Relative quantity of Weight of Animal.	Loss of Sensation Begun.	Loss of Sensation at its Height.	Amount of Loss of Sensation.	Sensa- tion begun to Return.	Loss of Sensa- tion Lasted.	General Weak- ness Begun.	At its Height.	Amount of General Weakness.	General Weakness begun to Improve.	General Weak- ness Lasted.	
	gm.	grn.							min.	hrs. min.	Complete.	Died.	min.	
Apr. 23	31	$\frac{1}{2}$	$\frac{1}{957}$	Immediate.	Immediate.	Complete.	...	...	2	1 20	Complete.	Died.	...	No stage marked,
"	15 $\frac{1}{2}$	$\frac{1}{2}$	$\frac{1}{717}$	"	24 min.	"	...	...	9	1 20	"	"	...	"
"	14	$\frac{1}{2}$	$\frac{1}{648}$	"	1 h. 40 min.	"	...	...	8	1 40	"	"	...	"
"	19	$\frac{1}{2}$	$\frac{1}{879}$	"	Immediate.	"	...	...	7	1 0	"	"	...	"
"	13	$\frac{1}{2}$	$\frac{1}{602}$	8 min.	1 h. 20 min.	"	...	...	18	1 2	"	"	...	"
Average, .			$\frac{1}{800}$		40				7.4	80				

Iodide of Sodium.

Date.	Weight of Frog.	Dose of Salt.	Relative quantity of Weight of Animal.	Loss of Sensation Begun.	Loss of Sensation at its Height.	Amount of Loss of Sensation.	Sensa- tion begun to Return.	Loss of Sensa- tion Lasted.	General Weak- ness Begun.	At its Height.	Amount of General Weakness.	General Weakness begun to Improve.	General Weak- ness Lasted.	
	gm.	grn.							min.	hrs. min.	Complete.	Died.	min.	
Apr. 24	18 $\frac{1}{2}$	$\frac{1}{2}$	$\frac{1}{850}$	Immediate.	Immediate.	Almost com.	4 min.	7 min.	Immed.	10 min.	Decided.	...	4	...
"	23 $\frac{1}{2}$	$\frac{1}{2}$	$\frac{1}{725}$	"	"	Complete.	...	10	"	Immed.	Complete.	...	...	...
"	17	$\frac{1}{2}$	$\frac{1}{787}$	"	"	"	...	4	"	"	No loss of general power.	...	...	...
"	19	$\frac{1}{2}$	$\frac{1}{879}$	"	"	"	5	15	"	Immed.	Complete.	...	3	...
"	23	$\frac{1}{2}$	$\frac{1}{710}$	"	"	"	2	5	"	No general weakness.	Complete.	...	...	...
"	26	$\frac{1}{2}$	$\frac{1}{802}$	"	"	"	7	20	"	Immed.	Complete.	...	2	...
"	32	$\frac{1}{2}$	$\frac{1}{739}$	"	"	"	4	17	"	"	"	...	2	...
"	30 $\frac{1}{2}$	$\frac{1}{2}$	$\frac{1}{641}$	"	"	"	9	25	"	In few seconds.	"	...	2	...
Average, .			$\frac{1}{804}$				5	12.7					2.6	

We first draw attention by the very marked difference between the effects of potassium and sodium salts. The difference in degree between the action of the two sets of salts is so great as hardly to admit of comparison. Thus the total effect of sodium salt was very slight, and in the main corresponded to the primary transient effect induced by potassium salts.

We append in the following table the average of our observations with sodium salts:—

	Loss of Sensation begun to Return.	Loss of Sensation Lasted.	Voluntary Power completely Restored
Chloride of Sodium	5·2 minutes	11 minutes	2·5 minutes
Bromide of Sodium	3 minutes	4·8 minutes	2·2 minutes
Iodide of Sodium	5 minutes	12·8 minutes	2·6 minutes

Far more powerful effects were produced with the corresponding potassium salts. Thus in by far the larger proportion of our observations there occurred immediate loss of sensation, which increased and became complete in a very variable time. General weakness soon set in, and steadily progressed till it became complete, and in almost every instance the animal died.

The following table shows the average of our results with potassium salts:—

	Loss of Sensation Complete in	General Weakness Begun.	Complete Paralysis.
Chloride of Potassium	18 minutes	6·5 minutes	40 minutes
Bromide of Potassium	8·3 minutes	...	55 minutes
Iodide of Potassium	...	7·4 minutes	80 minutes

Thus whilst paralysis from sodium salts lasted only three minutes, the potassium salts induced the same early paralysis, but on recovering from this primary condition, general prostration soon set in, and gradually progressing, soon became complete, the animal recovering only in three instances.

From the preceding table we see that chloride of potassium in about the same relative dose to the weight of the frog,

produces complete paralysis quicker than the bromide, and the bromide than the iodide; in other words, the chloride is a more powerful paralyser than the bromide, and the bromide than the iodide. We draw attention to the fact that the relative amount of potash is greater in the chloride than in the bromide, and in the bromide than the iodide, so that in order to administer the same quantity of potash, the salts must be given in *about* this ratio—

Chloride.	Bromide.	Iodide.
1	1·5	2

On referring to the preceding table, it is evident that the difference in the time each salt took to produce complete paralysis stands in much the same ratio as the proportion of potash in its composition. In the subjoined table we give the average proportionate dose to the weight of the frog, and the average time each salt referred to produce complete paralysis :—

	Chloride.	Bromide.	Iodide.
Average proportionate dose, .	$\frac{1}{821}$	$\frac{1}{736}$	$\frac{1}{800}$
Time of complete paralysis, .	40 minutes	55 minutes	80 minutes

Thus, to summarise our results :—Inasmuch as these three potassium salts produce the same symptoms in the same order with a progressive rapidity, each in proportion to the amount of potash in its composition, and further, as the corresponding sodium salts produce different effects, we are bound to conclude, with Guttman, that the influence of potash salts on the nervous system of frogs depends wholly on the potash, uninfluenced by the acid combined with it.

We now draw attention to the difference between the action of bromide of potassium and bromide of sodium on the nervous system. The careful observations of various experimenters, Eulenberg, Guttman, Lewisky, Bartholow, and others, prove that the chief effect of bromide of potassium is to diminish or to destroy the reflex power in the cord and in the afferent nerves. From our own experiments it is evident that these effects depend entirely on the potassium, and are

common to all potassium salts. Now, the efficacy of bromide of potassium in epilepsy is generally explained by its depressing power on the reflex function of the cord, a conclusion mainly based on the action of this salt on frogs. The grounds for this conclusion must be erroneous, since the depressing effect on the nervous system produced by bromide of potassium are common to other potassium salts, and yet these possess no similar action in epilepsy. Moreover, bromide of sodium is equally, or almost equally, efficacious in epilepsy, and yet it has no depressing effect on the nervous system comparable to bromide of potassium, we must conclude, therefore, that the effects of bromide of potassium on frogs fail to show us how this salt subdues epilepsy.

We may add, that our experiments with bromide of sodium confirm the observations of Laborde, who found that the sodium salts, even in double the dose of the bromide, did not produce any characteristic symptoms in the frog, the guinea-pig, or the dog.

From these experiments we arrived at another curious conclusion—that a salt acts mainly or exclusively, not as an entity, but in virtue of one of its constituents, on some organs, whilst it acts in virtue of its other constituent on other organs. Thus in the case of iodide and bromide of potassium, their effects on the nervous tissues depend entirely on the potassium, the iodine and the bromine playing no part. On the other hand, the iodine affects the skin and the mucous membranes, especially of the nose and eyes, and the bromine also affects the skin. Iodides cause coryza and a peculiar acne, and bromides induce a characteristic acne.

As iodides and bromides affect the skin, and iodides affect both the skin and the mucous membranes, especially of the nose, whilst potassium salts other than the iodides and bromides produce no such effect, it is clear that the coryzal and cutaneous symptoms are due to the iodine and bromine. It is true that iodide of sodium or ammonium are less liable to produce iodism than the potassium salt, and in these cases we are forced to admit that the sodium or ammonium must exercise some modifying influence on the iodine, still it is the iodine that acts, the sodium or ammonium only lessening its influence. Thus a salt

which probably undergoes no chemical change in the body acts on one structure solely through its base, and on another structure solely through its acid constituent.

Our investigations show that the chloride, bromide, and iodide of potassium affect the same parts of the nervous system of frogs, and in the same order; that sensation is first impaired or destroyed, with weakening or loss of the reflex functions, of course, ensuing. In a short time voluntary power declines, but it persists in natural or considerable degree when sensation is greatly diminished or destroyed. At last voluntary power is also lost. How is sensation impaired or destroyed? By the action of the potash salt on the afferent nerves, on the sensory tracts of the cord, or on the sensory centres in the brain? Our observations do not enable us to answer all these questions; but as in a former paper we find that the local application of any of these salts destroys sensation when applied to the skin, we suggest that it probably acts, in part at least, on the terminations of the afferent nerves, even when administered either by the mouth or hypodermically.

It is true that in our immersion experiments the iodide produced greater loss of sensation than the bromide, and the bromide than the chloride, the very reverse happening after the internal administration. Thus, after two minutes' immersion, the loss of sensation continued in the leg on an average—

Chloride.	Bromide.	Iodide.
117 minutes.	135 minutes.	190 minutes.

ON THE PHYSIOLOGICAL ACTION OF THE BULB
OF THE BUPHANE TOXICARIA OR HEMANTHUS
TOXICARIUS; AMARYLLIDACEÆ.

By SYDNEY RINGER, M.D.

PROFESSOR OF MEDICINE AT UNIVERSITY COLLEGE, LONDON,

AND

E. E. MORSHEAD, L.R.C.P.,

ASSISTANT TO THE PROFESSOR OF MEDICINE AT UNIVERSITY COLLEGE,
LONDON.

A FEW specimens of the large South African poisonous bulb, *Buphane toxicaria*, were sent to the Royal Gardens, Kew, and Mr. Thiselton Dyer kindly gave us one to test the physiological action of the plant. The Hottentots use this plant to poison their arrows. It is highly poisonous to cattle. Mr. Gerard prepared for us an extract, from which he obtained an alkaloid, the extract yielding about 1.75 per cent. of it.

In the first series of experiments we used the extract.

On April 1st we injected under the skin of a cat seven minims of a 1 in 5 solution of the extract. In about twenty minutes this made the animal dull and a little sleepy. An hour from the first injection we administered hypodermically 8 minims of the solution, which increased the drowsiness and produced decided weakness, so that in walking the cat rolled somewhat; the hind were weaker than the front legs, and the animal became so drowsy that when left to itself it fell asleep and nodded.

Next day we injected the same cat hypodermically with 8 grains

of extract (50 minims of the 1 in 5 solution). This caused slight weakness, twitching of the skin, retching and vomiting.

On April 5th we injected into the same cat 20 grains of extract which caused drowsiness, great weakness, especially of the hind limbs, though throughout the experiment the cat could walk, but it lay down with its head on the table. On the slightest irritation, as tapping the back, or even a loud noise, the whole body started and jerked. The pupils were dilated, but acted to light, and the mouth became dry. Sight seemed affected, and general sensation became impaired.

We next injected 27 grains of extract, and produced still more marked symptoms, nausea and retching, strong semi-tetanic twitchings and startings on the slightest irritation or from noises, and at one time the twitchings were almost incessant.

The animal grew so weak that it could scarcely stand, and as the weakness progressed the twitchings diminished. The weakness was most evident in the hind part of the body. Sensation was impaired. The startings were produced much more easily on irritating the anterior than the posterior part of the body. The pupils became widely dilated with loss of sight. The mouth was dry; the respiration much hurried and very shallow, at one time being 78 in the minute. The cat was drowsy. In four hours the cat had nearly recovered and next day, except being rather dull, it was quite well again.

These experiments show that this bulb produces drowsiness, general weakness, tremors, heightened reflex irritability, so marked that stimulation causes strong jerkings of the whole body, impaired sensation, dilatation of the pupil with dimness of vision, dryness of the mouth, nausea and sickness, hurried and shallow breathing.

Two experiments on frogs show that the extract, in large doses causes general paralysis and tetanus.

We injected under the skin of a frog one grain of the extract, being $\frac{1}{640}$ part of the animal's weight.

This produced slight weakness which passed away in an hour. In 104 minutes slight tetanic startings set in; on hopping the body of the whole animal jerked slightly, the legs were slightly extended, the feet expanded. The frog's movements, too, were stiff and awkward. The tetanus slightly increased, but though distinct, was never severe. It continued about 72 hours, and the animal had quite recovered. To another frog we administered $\frac{1}{164}$ part of its weight of extract, and in ten minutes the animal

became weak ; in 34 minutes tetanus began, and both paralysis and tetanus increased till the tetanus became strong and persistent, but the paralysis became complete. Twenty-four hours after death we opened the chest and found the heart stopped in wide diastole. Slight stimulation caused the heart to beat thoroughly 20 in the minute, though after some minutes the contractions again ceased.

These experiments on frogs, confirm therefore, the experiments made on the cat. With the cat we produced great general weakness with slight tetanic twitchings. In frogs the drug induces the same symptoms, but with much more marked tetanus.

We next investigated what structures were affected by hemanthus. We first experimented to ascertain whether the tetanus is due to the action of the poison on the brain, cord, nerves or muscles.

In two experiments we injected, in each case, a grain and two-fifths of the extract under the skin of the frog. Then on the onset of tetanus we destroyed the brain, and still the tetanus became well marked. Next we divided the sciatic nerve of one leg, and found that tetanus could not be induced in that limb, showing that the tetanus is not caused by the action of the poison on the nerves or muscles, and that the tetanus is not due to the action of poison on the brain ; since tetanus occurs after destruction of that organ, and must therefore be spinal.

We next experimented to ascertain what structures are implicated when hemanthus acts as a paralyzer ; whether through the brain, spinal cord, nerves or muscles.

As hemanthus destroys reflex action as well as voluntary power, and even after the brain is destroyed, it is evident that it paralyzes by its action either on the cord, the motor nerves or the muscles.

On April 17th we poisoned a moderate-sized brainless frog by injecting seven minims of the 1 in 5 solution of extract, and when complete paralysis set in we exposed the sciatic nerve and muscles, and tested these with the interrupted current. We found

that a very weak current applied to the nerve caused the muscles to contract strongly, and that a weak current applied directly to the muscles stimulated them to strong contraction.

April 17th.—Next we injected under the skin of a frog weighing 25 grammes three grains of extract. In 40 minutes it began to grow weak, and then general paralysis and tetanus simultaneously progressed, so that at the end of an hour the animal could just crawl a little, but if tapped the shock induced decided but not very strong tetanus extension of the legs. Next day, 17 hours from the commencement of the experiment, we found the animal quite paralyzed. We then exposed the sciatic, and muscles of the leg, and found that a weak galvanic current caused the muscles to contract strongly, but the sciatic nerve itself was completely paralyzed.

Since the application of a weak current of electricity to the sciatic nerve, after complete paralysis induces strong muscular contraction we conclude that the paralysis is not due to paralysis of the motor nerves ; and as the muscles also contract energetically on the direct application of a weak current of electricity, it is equally apparent that the paralysis is not due to paralysis of the muscles ; hence we must conclude that hemanthus paralyzes by its action on the spinal cord.

Although the preceding experiments, we think, prove that hemanthus paralyzes by its action on the spinal cord, we determined to perform the following supplementary experiments, especially as they enable us to decide whether hemanthus possesses likewise a paralyzing action on the motor nerves, though it must needs be a far weaker action than this agent produces on the cord ; moreover these experiments serve to show whether the paralysis of reflex action is due to the action of the poison on the sensory nerves, preventing the impressions reaching the cord.

We injected the extract under the skin of the back close to the lymph hearts, and as soon as tetanic symptoms set in, that is in about forty minutes, we destroyed the brain, cut through the

ACTION OF THE BUPHANE TOXICARIA.

heart, and divided the sciatic nerve of the right leg, to prevent the exhaustion of the nerve and muscle by tetanic contractions.

We then prepared some test frogs. We destroyed the brain, cut through the heart, and divided the right sciatic nerve so that the condition of the test frogs should be, in all respects, identical with that of the poisoned frogs except the poisoning. Then we tested with electricity the conductivity of the sciatic nerve and the contractibility of the muscles thrice daily, at 9 A.M., 1 P.M. and 6 P.M. First we tested the sciatic nerve through the skin, so that its function might not be impaired by exposure to the air; and when the nerve so treated ceased to conduct, we exposed it, and, having isolated it on glass, tested it.

THE ACTION OF EXTRACT OF HEMANTHUS ON THE MOTOR NERVES AND MUSCLE.

Date	Brain destroy'd, heart cut through and sciatic nerve divided after poisoning.	Amount of extract injected.	Weight of frog in grammes.	Right sciatic nerve ceased to conduct in.	Muscles of right leg ceased to contract.
Apr 18.	39 mins.	3 grains.	20 grammes.	25 hours.	
22.	35 mins.	3 grains.	26 grammes.	28 hours.	39 hours.
22.	55 mins.	3 grains.	34 grammes.	30 hours.	39 hours.
25.	30 mins.	3 grains.	25 grammes.	38 hours.	48 hours.
25.	43 mins.	3 grains.	31 grammes.	30 hours.	35 hours.
			Average	30.2.	40.5.

TEST FROGS.

Apr 18.				34 hours.	72 hours.
22.				40 hours.	83 hours.
25.				34 hours.	82 hours.
				49 hours.	49 hours.
			Average	39.2.	71.5.

We abstract the following averages from the preceeding table:

The sciatic nerve ceased to conduct.	In poisoned frogs in 40 hours.	In test frogs in 39 hours.
The muscles ceased to contract to a strong galvanic current.	30 hours.	71 hours.

We conclude that extract of hemanthus paralyses the motor nerves and muscles in a slight degree: The dose of alkaloid administered was small, for we used three

grains of extract, and the extract contains only about $1\frac{3}{4}$ per cent. of alkaloid. We shall, therefore, test with larger doses the action of the alkaloid on the motor nerves and muscles.

Before, however, we are justified in concluding that hemanthus paralyzes chiefly through its action on the cord, we must be certain whether it exercises any influence on the afferent nerves; for if it paralyzes these, then no impressions could reach the cord, and we could account for the general loss of reflex action by the paralysis of the afferent nerves. We must ascertain too whether hemanthus paralyzes the heart, and in this way arrests the circulation; for if so, paralysis of the spinal cord may be due to the arrest of circulation, and not to the direct action of the poison on the cord. To decide these questions we performed the following experiments:

We destroyed the brain, then ligatured the right femoral vessels, next placed a tight ligature around the muscles of the upper part of the thigh under the skin, taking care to exclude the sciatic nerve, and then injected three grains of extract into the left axilla. The frog became slowly paralysed, and when paralysis became complete we found that pinching the toes or calf of the right ligatured leg failed to excite any reflex action.

On April 29th we somewhat modified the experiment. After destroying the brain we tied the right femoral artery and vein of a moderate sized English frog, and then injected fifteen minims of the 1 in 5 solution of extract under the skin of the left axilla. In twenty-eight minutes tetanus commenced and progressed *pari passu* with general paralysis, and in two hours and ten minutes the animal was completely paralysed, so that mechanical stimulation of *either* extremity excited no reflex action. The paralysis progressed equally in both hind legs. In this experiment ninety minutes after complete paralysis and in the foregoing experiments in thirty minutes we opened the chest and found the heart beating fairly well at fourteen per minute.

These experiments prove that the loss of reflex action is not due to paralysis of the sensory nerves, for stimulation

of the ligatured protected leg failed to excite reflex action. Moreover the paralysis of the spinal cord is not due to arrest of the circulation from cardiac paralysis, for after complete paralysis we found the heart beating at twelve per minute.

ACTION ON THE FROG'S HEART AND VAGUS.

Dr. Burdon Sanderson kindly tested for us the action of extract of hemanthus on the heart and vagus of the frog:

After exposing the vagus just as it issues from the skull and exposing the heart without opening the pericardium he applied the electrodes to the vagus, and as usual the heart was arrested for several beats. After testing the effect of galvanic stimulation of the vagi three times with the same result, he injected three grains of extract, diluted with water, under the skin of the back and then tested the effect of faradisation of the vagus, and found that even the strongest current from a one-celled Daniel's battery with Du Bois Reymond's induction coil failed in any degree to affect the heart's contractions. He then opened the pericardium and applied the electrodes to the junction of the sinus with the auricle which slightly accelerated the heart's contractions during contact, but this acceleration ceased on removal of the electrodes, when perhaps a slight slowing for a second or two occurred, so slight, however, that we cannot be sure of it.

This experiment we repeated with exactly the same result; but we poisoned the animal with one grain only of the extract.

We next tested the action of hemanthus on the intracardiac inhibitory apparatus.

We poisoned two brainless frogs by injecting under the skin of the back a grain and two grains respectively. An hour afterward we opened the thorax and pericardium, and then turning the heart over exposed the sinus as it enters the auricle. In this operation, in the first experiment, we unfortunately divided the abdominal vein. The heart was contracting badly at 32 per minute. We applied the electrodes to the groove between the sinus and the auricle, without in any way modifying the contractions.

In the second experiment, May 8th, 34 minutes after poisoning we exposed the heart, and found it beating well at 18 per minute. We then applied the electrodes to the sinus, and this raised the beats to 26, but rendered them feeble. We repeated the application in ten minutes with the same result. After removing the electrodes a slight pause occurred, but far less than happens after the application of the electrodes to an undrugged heart.

On another occasion we exposed the heart of a frog whose brain and cord were destroyed, and then applied the electrodes to the groove between the sinus and the auricle, and ascertained the strength of the current adequate to powerfully inhibit the heart. We then applied a solution of the extract to the heart, and in a few minutes found that a current of the same strength failed to arrest or slow the heart, but made the beats more frequent. On increasing the current to the battery's full strength, slight slowing, we think, followed for one or two beats, succeeded by accelerated action.

These experiments lead us to conclude that hemanthus paralyzes the vagus, and greatly weakens and even paralyzes the intra-cardiac inhibitory apparatus.

These experiments show that large doses, as two or three grains of extract, given hypodermically to a moderate sized frog slows and weakens the heart, but after several hours it still continues to beat moderately well at twelve to fourteen per minute.

We next tested whether hemanthus antagonizes the action of muscarin on the frog's heart. We exposed the heart of a brainless frog, and applied a 1 in 5 solution of extract of *amineta muscaria* in the neighborhood of the sinus and auricles. When the heart became greatly slowed and weakened, or altogether arrested, we applied the extract of hemanthus. We give the results in the following table:

In a previous communication* we showed that one drug may oppose the action of another drug though each produces the same effects. Thus pilocarpine antagonizes the action of muscarin on the frog's heart. As hemanthus

* *Journal of Physiology*, vol. ii.

ACTION OF THE BUPHANE TOXICARIA.

affects the heart like atropia, we were anxious to see if atropia would antagonize the effect of hemanthus. We give two experiments showing that atropia does not antagonize the action of hemanthus.

Date	After application of muscarin heart reduced from to.	Strength of contraction.	After application of extract of hemanthus, heart beats rose to.	Strength of beat	
May 12.	48 to 8 in eight minutes.	Very feeble. auricle ceased.	28 in 3 minutes to 34 subsequently.	Very good.	Three hours after the heart beat fairly well at 34. Next morning the heart had stopped. widely distended but quite pale.
13.	48 to 0 in two minutes.	stopped.	34 in 4 minutes.	Fairly good.	
13.	48 to 0 in seven minutes.	stopped.	24 in 9 minutes.	Poor.	

On May 8th we exposed the heart of a brainless frog, and applied a 1 in 5 solution of hemanthus to the sinuses and auricles. This reduced the heart's beats from 56 to 20, and greatly enfeebled their strength. We then applied a small quantity of a 1 per cent. solution of sulphate of atropia; the contractions became stronger, but in the following fifteen minutes the beats fell to 14.

On the following day we repeated the experiment. The extract of hemanthus reduced the beats from 55 to 24, and weakened them. After the application of the solution of atropia the beats continued to grow less frequent, and in twenty minutes had fallen to 14. The atropia appeared to exercise little or no influence on the strength of the contractions; perhaps they were a little stronger, though if so the improvement was scarcely manifest.

ACTION ON MAN.

A man swallowed a grain of the alkaloid hemanthia, which produced only slight dryness of the mouth, so that this experiment would indicate that on man hemanthia is far less powerful

than atropia. We shall see presently that the reverse is the case as regards cats.

A man took a grain of the extract every half hour for six doses and then four hourly doses. The only apparent effect was dryness of the mouth, causing him to drink very frequently.

Next day, May 2d, the same man took twelve grains in five hours, which produced more dryness of the mouth and thirst, with rather free perspiration, and he said he passed more water than usual.

On May 3d, after taking thirty-three grains of extract in three hours and a half, he complained of great dryness of the mouth and parched lips. The lips looked very dry, and to the touch the tongue felt a little dry. He was very thirsty. At the end of three hours, when he had taken twenty-nine grains of extract, his hands were slightly moist. He passed, he said, a very large quantity of water; indeed he had to urinate nearly every half hour. He filled two utensils with urine. The increased urine was not due to the thirst, for he was not allowed any drink while this experiment was going on. This large dose neither dilated his pupils nor caused headache, and, indeed, produced no symptoms other than those mentioned.

On May 5th he took 50 grains of extract, which produced only dryness of the mouth with increased flow of urine, as the following table shows :

Hour.	Quantity of Urine.	Took Medicine.	Amount.
11 to 12	2 oz.	Dinner at 12:30, P. M. 2 P.M. 2:30 3 3:30 4 4:30 5 5:30 6 6:30	gr. 5 " " " " " " " " "
12 to 1	1½ oz.		
1 to 2	3 oz.		
2 to 3	2½ oz.		
3 to 4	2 oz.		
4 to 5	4 oz.		
5 to 6	6 oz.		
6 to 7	4 oz.		
7 to 8	4 oz.		

He passed, therefore, in the first three hours 6½ oz., and 22½ oz. in the six hours during which he took hemanthus; that is to say, the medicine nearly doubled the quantity of urine; and if we exclude the first two hours after commencing the medicine

when its diuretic effect had probably scarcely begun, we find the drug rather more than doubled the quantity of urine.

The increase in the urine was certainly not due to increased drink from thirst, except at dinner, for the patient had taken no fluid, and then only his usual quantity.

These experiments on man, therefore, show that hemanthus dries the mouth and increases the urinary secretion ; and we may here state that each of the cats we experimented on passed water freely. The effect on the skin secretion is doubtful, for this man, always a free secreter, perspired during each of these experiments. Hence, if hemanthus does check perspiration it manifests this property in a weaker degree than its influence on the salivary secretion.

A man received a grain of nitrate of hemanthia hypodermically. In about half an hour this dried the mouth, produced faintness and the patient became childish or idiotic. These symptoms lasted about half an hour.

Another man received the same dose which induced the same symptoms, but in this instance the drug produced greater weakness, so that he could scarcely move a limb or raise his head from the pillow. He perspired freely. Symptoms lasted about half an hour.

In these observations with the alkaloid given hypodermically, the pupil and pulse remained unaffected.

Mr. Gerrard prepared for us a one in twenty solution of the sulphate of hemanthia.

Mr. W. H. Neale tested its action on the pupil of eleven persons, applying in each instance a single drop to the eye.

He finds that the alkaloid dilates the pupil quickly and widely, but the dilatation soon passes off ; on the average in five and a half hours.

The results of Mr. Neale's observations is shown in the following table :

ACTION OF THE ALKALOID (HEMANTHIA SULPHATE) ON THE PUPIL.

	Dilatation begun in	Amount of Dila- tation.	Dilatation lasted
	15 minutes.	widely dilated.	5 hours.
	20 minutes.	"	7 hours.
	25 minutes.*	slightly.	5 hours.
	15 minutes.	widely.	6 hours.
	15 minutes.	"	7 hours.
	15 minutes.	"	6 hours.
	25 minutes.	moderately.	5 hours.
	15 minutes.	"	7 hours.
	15 minutes.	"	5 hours.
	15 minutes.	widely.	5 hours.
	25 minutes.	moderately.	4 hours.
Average.	18 minutes.		5.6 hours.

*Only a part of the solution entered the eye.

Summary of conclusions :

In warm-blooded animals hemanthus causes drowsiness, general weakness, tremors and tetaniform startings, impaired sensibility, dilatation of the pupils, dimness of vision, dryness of the mouth, hurried and shallow breathing, nausea and sickness.

In frogs it causes paralysis and tetanus; and paralysis precedes tetanus.

Tetanus is due to the action of the poison on the spinal cord.

Paralysis is due chiefly to the action of the poison on the spinal cord.

Hemanthus paralyzes, in a slight degree, the motor nerves and muscles.

Hemanthus paralyzes the vagus and the intra-cardiac inhibitory apparatus.

It slows and weakens the heart of frogs.

It antagonizes the action of extract of muscaria.

Atropia does not antagonize the effects of hemanthus on the frog's heart.

In man it produces general weakness, delirium, dryness of the mouth, increased urinary secretion; topically applied it dilates the pupil.

The action of this amaryllidaceous plant, *hemanthus toxicarius*, corresponds very closely, if, indeed, its behavior be not identical with that of the alkaloid from the common Daffodil (*Narcissus*), a member of the same order. In warm-blooded animals both dilate the pupil, whether administered internally or topically applied. Both dry the mouth, produce general weakness, tetaniform twitchings, nausea, sickness and hurried breathing.

Both antagonize the action of extract of muscaria on the frog's heart.

Hemanthia, however, acts, like *narcissia*, only when it is obtained from the bulbs of the plant when in flower. The action of this alkaloid derived from the bulbs a few weeks or months after flowering differs singularly from the action of the alkaloid just referred to. This alkaloid extracted after flowering causes salivation, contracts the pupil when internally administered and slightly dilates it only when topically applied.

The action both of *narcissia* and *hemanthia* is in many respects similar to that of *atropia*, which also dilates the pupil when internally administered and especially when topically applied, dries the mouth, produces weakness, drowsiness, tetaniform twitching in warm-blooded animals, well-marked tetanus in frogs, nausea and vomiting; in cats, hurried breathing, accelerated pulse.

Dr. Fraser has shown that *atropia* produces tetanus in warm-blooded animals, and we were anxious to ascertain how far the effects of *hemanthia* and *narcissia* correspond to those of *atropia*; we therefore administered some *atropia* hypodermically to a cat, and produced exactly the same tetaniform twitching as that which follows the administration of *narcissia* or *hemanthia*.

We administered sulphate of *atropia* hypodermically to the same cat to which we had given extract of *hemanthus toxicarius* to ascertain to what extent the effects of these two drugs are alike. Dur-

ing two hours we administered $\frac{7}{8}$ of a grain of sulphate of atropia, in seven injections of gr. $\frac{1}{8}$. The first dose $\frac{1}{8}$ gr., produced weakness, drowsiness, dilatation of pupils and dry mouth. When the animal had received $\frac{7}{8}$ grain, these symptoms did not increase, but on tapping the back elicited slight twitching. Next day we injected, at first two grains, which produced sleepiness and slight twitching, twenty minutes afterward we injected another grain which increased the twitchings, though the animal could still walk. 134 minutes from the first injection, we gave another grain, making four in all; this dose produced drowsiness, much general weakness, tremors and tetanic startings induced by tapping the back, or pinching the skin, or by loud noises: in fact, the same symptoms which follow the injection of extract of hemanthus.

Whilst hemanthia and atropia have many properties in common, yet they differ from each other in the following respects. Hemanthia affects first and chiefly the brain and spinal cord, and in a less degree the salivary secretion and the pupil; for a moderate dose causes drowsiness, weakness and tetanic twitchings, whilst the mouth becomes only slightly dry and the pupil moderately dilated, but a larger dose dilates the pupil widely and makes the mouth very dry; on the other hand, a moderate dose of atropia widely dilates the pupil, makes the mouth quite dry, and enduces slight drowsiness, but weakness and tetanic twitching come on only when a very large dose, as four grains, is given hypodermically. As far as cats are concerned, hemanthia is a far more powerful alkaloid than atropia. Mr. Gerrard calculates that the extract of hemanthus yields $1\frac{3}{4}$ p. c. of alkaloid. Twenty and twenty-seven grains of this extract equal therefore to between $\frac{1}{4}$ and $\frac{1}{2}$ grain of alkaloid produced symptoms as decided as those induced by four grains of sulphate of atropia.

It is interesting to observe that whilst the members of the solanaceous order possess many properties in common, yet in certain members some of these properties, as the foregoing pages exemplify, are reversed.

The same remark holds with regard to some of the amaryllids.

Thus atropia, hemanthia, narcissia from the flowery bulbs whether topically applied or taken by the the stomach, dilate the pupil and arrest most secretions. The remaining number, narcissia from bulbs when flowering is over, pituria, nicotine, affect the pupil differently; narcissia contracting the pupil when given internally and only slightly dilating it when topically applied; pituria contracting the pupil when internally administered, but dilating it when topically applied, whilst nicotine, whether it is given by the mouth or topically applied, contracts the pupil; moreover all these plants increase most of the secretions.

This summary shows the respective properties of Solanaceous and Amaryllidaceous plants.

Atropia dilates the pupil, dries the mouth, produces general weakness, tetaniform starting in cats, well marked tetanus in frogs, impaired sensibility, drowsiness, nausea and vomiting (cats), hurried breathing, accelerated pulse.

It paralyzes the motor nerves, their terminations first; it paralyzes the spinal cord, and the extra- and intra-cardiac inhibitory apparatus.

It affects but slightly the voluntary muscles.

Hemanthia dilates the pupil, dries the mouth, produces general weakness, tetaniform startings in cats, well marked tetanus in frogs, impaired sensibility; it causes drowsiness, nausea and vomiting, hurried breathing.

It paralyzes the cord and probably the motor nerves, and produces a very slight effect on the voluntary muscles.

Narcissia from flowering bulbs, whether applied externally or given internally, dilates the pupil, dries the mouth, produces general weakness, slight twitchings and startings, drowsiness, nausea and retching, accelerated pulse.

Narcissia after flowering is over, internally slightly contracts pupils, topically applied dilates pupil, but not

strongly. It produces copious salivation, probably increases cutaneous secretion, general weakness, strong muscular and tetaniform twitchings, nausea and sickness, drowsiness, hurried breathing, slight acceleration of pulse.

Pituria locally applied dilates the pupil, internally administered contracts and in very large doses (as in cats), dilates the pupil, salivates, sweats, produces general weakness, strong tetanic twitchings, drowsiness, nausea and vomiting, hurried breathing.

Nicotine administered internally or applied topically contracts the pupil; given internally in very large doses it dilates the pupil, it salivates and sweats, and produces general weakness, strong tetanic twitchings, and stiffening of the extremities on walking or running, well marked tetanus in frogs, nausea and sickness, hurried breathing, accelerated and weak pulse. It paralyzes the motor nerves, their terminations first, it next paralyzes spinal cord; and produces no effect on voluntary muscle.

Each of these alkaloids produces general weakness, tetaniform startings, and several produce *tétanus* in frogs. They cause drowsiness, nausea and vomiting, hurried breathing and accelerated pulse. Nicotine in one respect is an exception to this statement, for it does not apparently produce drowsiness. At all events the symptom is not noticed in papers treating of the action of nicotine, and in one observation we made on a cat drowsiness was certainly absent.

We may point out that those substances which have been investigated concerning their influence on the nervous and muscular system all correspond in their physiological action; thus atropia, hemanthia and nicotine paralyze the spinal cord and motor nerves but leave the voluntary muscles unaffected.

Some writers believe that pituria and nicotine are identical. We are inclined to think that whilst very closely

allied they are not identical, for we find that pituria topically applied dilates the pupil, whilst Kröker (quoted in Wood's therapeutics,) finds that nicotine topically applied contracts the pupil. Moreover, we find that nicotine produces in cats far less tetanic twitchings than pituria, but other observers appear to have obtained from nicotine a greater degree of tetanic twitchings than we met with. We find that nicotine produces that peculiar stiffness of the limbs seen when the cat walks or runs, which is so marked after pituria. In our experiment it occurred without any tetanic twitchings on tapping the cat's back or other part.

We draw attention to the fact that the drugs hitherto investigated that affect the pupil also modify secretion. The following table is arranged to exemplify the action of these drugs on the pupil:

Pupil dilators internally or topically applied.	Given internally, contract topically applied, dilate.	Given internally, contracts; topically, first contracts for short time, then dilates.	Pupil contractors internally or topically applied.
Atropia.	Muscarin.	Narcissia,	Physostigmia.
Hyoscyamia,		(from bulbs after flowering	Pilocarpia.
Daturia.		has ceased).	Nicotine.
Duboisia		Pituria.	Opium.
Narcissia (from flowering bulbs).		Gelsemia,	
Hemanthia.		(salivates cats.)	
Conium ???			

All those substances which dilate the pupil, whether used internally or topically, are arresters of most of the secretions. Those substances which contract the pupil, whether used internally or topically, increase most of the secretions.

There is a curious intermediate group the action of which when administered internally differs from its action when topically applied. The members of this group increase most of the secretions. Should further investigations confirm these conclusions, it appears that the influence of the internal administration of a drug on the pupil is a better indication of its effect on secretion than the topical application of the same drug. The foregoing table illustrates this fact.

It may be objected that opium, a contractor of the pupil, increases only the skin secretion whilst it checks other secretions, being in fact more an exception to than a corroboration of the rule we are attempting to establish. This no doubt is true and obliges us to modify our general conclusions.

With the exception of opium and its alkaloids all the substances in the preceding tables act probably directly on nervous structures in or near the eye, whilst opium probably affects the pupil through some part of the central nervous system; for, opium excepted, these substances when topically applied to the eye, all powerfully affect the pupil, and indeed thus applied affect it most readily and markedly. The topical effect corresponds to that induced by a very large dose given internally. The topical employment of opium on the other hand produces little or no effect, though the pupil becomes contracted when opium is given by the stomach. Therefore our general statement must run thus: That the action of a drug capable of affecting the pupil, through an intra-ocular nervous apparatus, affords an indication of the effect of the same agent on secretion.

In the preceding table we have not included picrotoxine, which Luchsinger has shown increases the cutaneous, salivary and lachrymal secretion, and we find too increases the salivary secretion. The effect of picrotoxine on the pupil does not appear to be satisfactorily determined.

The Husemanns, in their *Pflanzenstoffe*, say that it often contracts the pupils, which become dilated at the close of the poisoning.

If this statement is correct then picrotoxine conforms to the rule we have suggested. We have tested the local application of picrotoxine with a saturated solution, about 1 in 150 parts of water in large quantities, and frequently repeated to the eye, but without affecting it in any way.

THE ACTION OF VERATRIA ON THE VENTRICLE OF THE FROG'S HEART.

By SYDNEY RINGER, M. D.,

PROFESSOR OF MEDICINE AT UNIVERSITY COLLEGE, LONDON.

IN these experiments I used Roy's tonometer. In most cases I employed the entire ventricle; in some only the lower two thirds, the portion free from nervous ganglia.

I used dried bullock's blood dissolved in water and diluted with saline in the proportion of one part blood to two saline.

In some experiments the ventricle beat spontaneously; in others contractions occurred only on the application of an induction shock.

A number or the sign + is given in the charts, to indicate the application of an induction shock. The number indicates the place at which the coil stood. The series of rises under either a number or + are due to a single induction shock.

The traces read from left to right.

Since temperature modifies the action of veratria on the ventricle of the frog's heart, I shall describe, first, my results with a high temperature, between 80° and 90° F.; then with a moderate temperature, between 60° and 70° F.; and, lastly, with a low temperature of about 40° F.

Effect of veratria with a high temperature.

The effect of veratria is in many respects best manifested when the heart does not beat spontaneously, but only on excitation, as shown in trace i, taken when the temperature of the room was close on 90° F.

Veratria first prolongs the duration of the systole, so that the summit of the amplitude becomes rounded; and this is still better seen in traces taken in a cooler room, or when the blood is cooled by ice.

Next, each excitation produces two contractions, but the interval is so short that the diastole is incomplete and the two traces become partially blended. In many instances, after the first contraction, the heart bulges at some point, and the diastole does not affect the whole ventricle; there is, indeed, incoördinate action of the ventricle. Each excitation soon induces a still more prolonged effect, and we get three, four, or more contractions produced in the manner just now described. Some portion only of the ventricle dilates, sometimes a small portion, sometimes a larger, and then re-contracts; and the degree of the trace-fall depends on the size of the bulging. In a few minutes each excitation produces a prolonged contraction, or series of contractions, lasting from 30 to 120 seconds; then after the excitation the ventricle suddenly contracts and the trace suddenly rises, then falls, sometimes considerably, at other times slightly, and the trace shows the ventricle is beating very incoördinately; but as the effect of the excitation persists this incoördination becomes much less, and in some cases even disappears. After a larger dose the trace suddenly rises, then falls slightly, and remains at nearly the same height as a straight line for 30 or 40 seconds; then the line becomes wavy. Though the line appears straight, a lens will often show that it is wavy, but in some cases the

line is quite straight. After it has become wavy for a variable time it slowly falls toward its original position on the base line. When the trace forms a straight line or the undulations are very small a considerable movement is visible in the ventricle, consisting of rapid, small, peristaltic waves of dilatation and contraction, running generally from base to apex.

With a larger dose (trace i, *C*), after remaining at much the same height for many seconds the trace slowly falls toward the base line, giving a trace much like the fall in a tetanized skeletal muscle.

The duration of the effect depends on the interval between the excitations. If, as soon as the effect of one excitation is over another excitation is applied, the duration of the effect of the second excitation is much diminished. In fact, the duration of the effect is in proportion to the duration of the diastolic pause. (Trace i, *B*.)

The irregularities in the trace are best studied by examining the ventricle. One sees extreme incoördination, especially as regards dilatation. A portion dilates when the rest remains contracted, hence pouching occurs, and some pouchings contract before others.

In these and other traces that I have taken it is noticeable that although the form of irregularity varies in different experiments, yet in each experiment the irregularity observes much the same type (see traces ii and iii).

At the end of a prolonged effect of an excitation the veratria irregularity often becomes less, and a ventricle at first very incoördinate at last beats nearly or quite coördinately (see trace i, *B*).

The sustained contraction, much longer after a large dose, which occurs for a brief interval after each contraction, is not due, as some hold, to an altered physical condition, lessening the elasticity of the ventricle, but

is due to muscular contraction—is, in fact, a prolonged spasm.

1. Either spontaneously or after an excitation the ventricle at first remains contracted for a variable time, then very incoördinate contractions ensue, and at last the contractions become quite coördinate (see traces i, iii, iv), and the ventricle stops in diastole. This series of events could not be explained were the elasticity of the ventricle alone affected.

2. In some cases after a contraction the ventricle relaxes greatly, but not completely, and remains in this semi-relaxed condition, and a strong vermicular action sets in; after a time the ventricle suddenly and completely relaxes with cessation of the vermicular action. This course of events cannot be explained on the supposition that veratria simply lessens elasticity (see trace vii, *F* and *G*).

3. Pouching, now of one part and next of another, cannot be explained on the supposition that the changes in the ventricle are due to lessened elasticity.

We see, then, that veratria induces, first, a change in the ventricle, so that each contraction is prolonged, and the amplitude of the trace is broader and its summit rounder; next, a single excitation, instead of one response, induces two contractions (see trace i, *A.* iii, *B.*); in other words, each excitation produces an increased expenditure of force.

As the effect of veratria progresses (more speedily after a large dose), each excitation produces a prolonged series of contractions, lasting thirty or more seconds, and the ventricular action becomes extremely incoördinate. Veratria, then, increases not only the expenditure of force set free by each excitation, but it lessens or destroys the conditions which make the action of the ventricle coördinate. These effects veratria produces by its direct action on the muscu-

lar tissue, since they were obtained with the lower two thirds of the ventricle, a part free from nervous ganglia.

Temperature strikingly influences the action of veratria on the ventricle. A small dose greatly affects the ventricle at a moderate or high temperature, but at a low temperature produces no effect; and at a low temperature a large dose, whilst greatly increasing the duration of the contraction (increased expenditure of force), only slightly incoördinates the action. It is probable, therefore, that the temperature of fever modifies the influence of remedies, and that veratria affects the heart more powerfully in fever than in health.

The incoördinate action is produced mainly, if not exclusively, by incoördinate dilatation; one portion dilates and forms a pouch, whilst the rest remains contracted. After each excitation there is, first, a coördinate contraction, but then some portions *remain contracted longer than others*, so that irregular dilatation ensues.

Veratria, therefore, affects the heart much as it affects the skeletal muscles. With a skeletal muscle veratria enormously prolongs the contraction and yet longer its relaxation. When the relaxation is complete well-marked fibrillary contractions set in, lasting many seconds, but produce no shortening of the muscles. These effects are not due to the influence of veratria on the nervous system, for they occur, I find, when the motor nerves are completely paralyzed by curare. With the skeletal muscles, then, veratria produces an increased expenditure of force, with incoördinate action of the fibrillæ.

In the muscular tissue (as, indeed, in nervous and secretory tissues) we have not only the fuel whose combustion supplies the force to the tissue, but we have, besides, a mechanism to convert the liberated force into muscular motion, nervous action, or secretion. There must also be a mechan-

ism to regulate the amount of energy developed, and to co-ordinate the action of muscular and nervous tissues. A poison may affect the combustibility of the fuel, or the mechanisms, or both, and so paralyze a structure. Veratria, I venture to suggest, disorders the machinery, and so causes at first an increased expenditure of energy, then incoördinate action, and at last complete paralysis.

The action of veratria on muscle is in many respects comparable with the effect of strychnia on the spinal cord. Instead of a coördinated response of short duration, an excitation calls forth from a strychnized cord a prolonged and incoördinated action. The slightest excitation spreads throughout the cord and causes a general evolution of force, lasting a considerable time.

Like veratria on muscle, strychnia weakens or destroys those conditions in the cord which determine the amount of force evoked by an excitation; hence the prolonged effect of an excitation on the strychnized cord. At the same time, strychnia destroys the mechanism which coördinates action, so that the response is incoördinate.

Continued strong faradization affects the heart much like veratria. Under the influence of a strong interrupted current the ventricle becomes contracted, then small bulgings occur, sometimes at one portion and then at another, and these bulgings immediately contract again. After a time the bulgings increase in size, and then both systole and diastole become most irregular.

If a poison can cause incoördinate action by its direct action on the muscular tissue, and independently of its action on the nervous tissue, it is probable that disease of the muscular tissue may also cause muscular incoördination. The fibrillary twitchings in progressive muscular atrophy, which are so similar to the fibrillary movements after poisoning by veratria, are probably due to changes affecting

the muscular machinery; also some cases of irregular action of the heart are probably due to disease of the muscular substance, and not of the cardiac nervous apparatus.

Further, the lower two thirds of the ventricle, the portion free from nerves, contracts coördinately, spontaneously, or when excited; and this implies a coördinating mechanism which disease may destroy, and so produce incoördination.

Atropia in some respects antagonizes the action of veratria, for atropia stops or greatly lessens the irregularities, though the heart's action becomes much weaker.

Traces viii, viii (α), and ix, show the antagonizing effect of atropia.

Explanation of Plates.

Effect of veratria with a high temperature.

Trace i.—With the whole ventricle, which did not beat spontaneously. *A*, Effect of 5 minims of 1-in-500 solution of veratria added at the point indicated by the arrow. *B*, Nine minutes later. *C*, After an additional 20 minims of the solution.

Trace ii.—With the whole ventricle, which did not beat spontaneously. Well shows the effect of a single excitation, after a larger dose of poison. Here there are no undulations in the early part of trace following the excitation, even with the aid of a lens. After 40 minims of 1-in-500 solution.

Effect of veratria with a temperature between 60° and 70° Fah.

Trace iii was obtained with the lower two thirds of the ventricle, a portion of the heart free from nervous ganglia. It is a good instance of the effect of veratria when the temperature of the blood is between 60° and 70°. As the effects from this segment of the ventricle are the same as those which occur when the entire ventricle is used, it is evident that the veratria manifests its action on the muscular tissue.

As with a higher temperature, so veratria with a moderate temperature first prolongs each contraction. Then each excitation induces two contractions; but as the second contraction does not begin till the completion of the first, they remain dis-

tinct, instead of being blended, as happens when the temperature is higher. Next the trace becomes affected, as with higher temperatures, and need not be more fully described here. This portion of the ventricle did not beat spontaneously. *A*, Before veratria. *B*, After 5 minims of 1-in-500 solution. The + indicates the excitation. It is seen that each excitation induces two contractions. *C*, After a larger dose. *D*, After a still larger dose.

Trace iv.—With the whole ventricle. Shows the gradual development of the veratria effect. *A*, Before veratria. *B*, Five minims of 1-in-500 solution added at the point indicated by the arrow. *C*, Eighteen minutes after veratria. *D*, About forty minutes after veratria.

Trace v.—Shows the effect produced by a large dose at a moderate or high temperature. Each rise becomes broader, then coalesces with its fellow ; that is, one contraction begins before the previous one ends, and at last forms nearly a straight line raised high above the base line.

This trace was taken with the whole ventricle. At the arrow ten minims of 1-per-cent. solution of veratria was added.

I now give the effect of veratria, with blood cooled, by a freezing mixture, down to 8° or 10° Fah.

Trace vi.—With the whole ventricle. *A*, Before veratria and after the blood was cooled to about 8° to 10° Fah. *B*, About nine minutes after 15 minims of 1-per-cent. solution of veratria. *C*, About eighteen minutes after veratria. *D*, Later effect.

Sometimes even at a low temperature veratria in large doses incoördinates the ventricle, but in a far less degree than when the temperature is high. This is exemplified in trace vii, which also shows the alternating effect first of cold, then of heat, and then again of cold.

Trace vii.—With the whole ventricle. *A*, Temperature of blood 63° F. *B*, Temperature of blood 45° to 46° F. *C*, Two minutes after 15 minims of 1-per-cent. veratria solution. Temperature of blood 43° F. At first there occurred decided irregularity. *D*, About eight minutes after veratria. *E*, eighteen minutes after veratria. Temperature of blood 40° F. I then removed the ice-and-salt mixture. *F*, Thirty-six minutes after veratria. Temperature of blood 64° F. Here after the rise a decided fall took place, and for some time, eight to ten seconds, the trace remained at the same point, and then suddenly fell. Whilst it remained horizontal, and before the final sudden fall, very distinct frequent peristaltic action occurred, generally proceed-

ing from base to apex. After the final fall this ceased. *G*, forty-five minutes after veratria, temperature of blood 81° F. Here the tracing is the same as in the last, except that the primary fall was greater and the final fall very slight. I then raised the temperature of the blood to 86° F. and the heart's action grew very weak and infrequent. *H*, fifty-four minutes after veratria, blood 86° F. I then again applied the freezing mixture. *I*, Sixty-three minutes after veratria, blood 59° F. Here, again, after the primary fall and before the final fall, well-marked frequent peristalsis occurred. *K*, Seventy-four minutes after veratria, blood 41° F.

Tracings showing the antagonizing effect of atropia.

Trace viii.—With the whole ventricle, temperature of blood about 90° Fah. *A*, Effect of 5 minims of 1-in-500 veratria solution. At the point indicated by the arrow 10 minims of 1-per-cent. solution of sulphate of atropia were added. *B*, At the arrow other 10 minims of 1-per-cent. atropia solution added.

Trace viii (*a*). Temperature between 60° and 70° Fah. *A*, Before veratria. *B*, Effect of 5 and 10 minims of 1-in-500 solution of veratria. *C*, Shows the effect of atropia; at the arrow 20 minims of 1-per-cent. solution of sulphate of atropia added. *D*, Ten minutes later.

Trace ix.—With the whole ventricle, temperature of blood 66° Fah. *A*, Before veratria. *B*, After 30 minims of 1-in-500 solution of veratria. The notch in this trace was due to a broad peristaltic wave of dilatation and contraction, and shows that when this is large enough it affects the trace; at other times, when smaller, as previous traces show, the trace is unaffected. *C*, After 70 minims. *D*, After 10 minims of 1-per-cent. solution of sulphate of atropia. *E*, About a minute later.



tion, now in another, but in every case there has been some effect in both directions.

It was mentioned at the outset that the ligature was not always exactly in the auriculo-ventricular groove; this, however, does not introduce an error, for the action of the drugs was tested on a rhythmically contracting tissue, and this in all cases was secured.

The question now arises, are the two manifestations above mentioned intimately connected one with the other, so that action on the one necessarily involves action on the other? or may they be more or less dissociated from one another, and separately subject to influence? The former supposition, viz. that of an intimate connection underlying the dual manifestation, requires for proof evidence of such union in the shape of constancy of relation, both in kind and degree, *i.e.* qualitative and quantitative. If closely united, the evidence of such must be that they move together in *some* definite direction at *some* definite rate.

On the other hand, the proposition that they are dissociated requires the negative evidence of *absence* of any constant relation, qualitative or quantitative—the demonstration that they do not move together.

The consideration of this subject necessitates the use of *terms* in place of the phrases “value of each beat,” “frequency of contraction.” For the former the word *contractility*, as naming the underlying element, may be substituted; for the latter the term “*excitability*” has been selected. The term is not without objection, and must be taken in the wide significance of “*conditions antecedent to the contraction.*” These conditions are, of course, causal, but whether they be of the nature of “conditions generating the stimulus,” or “conditions preparing the contractile tissue for the stimulus, *i.e.* rendering the stimulus available,” must be left undiscussed. The terms being thus defined, we have to consider whether *excitability* and *contractility* must be associated or may be dissociated.

What do we actually find? In one case we note

increased frequency attending increased height of beat, in another increased frequency attending diminishing height ; and examples of this are to be found not only in the case of different hearts, but even in the same heart it may be found. Thus the ammonia salts, *e.g.* the chloride or bromide, frequently show a primary increase of frequency even during the stage of increased height of beat, and this increased frequency is not only maintained but may even go on increasing as the height of the trace steadily falls. Thus, there is no constant qualitative relation between *contraction rate* and *contraction height*.

Again, in one and the same heart we note as the effect of a drug at one time marked effect, say on excitability, with no appreciable effect on contractility ; a little later, and with no noticeable effect on excitability, the stress now falls on contractility.

Potash salts illustrate this very well. Thus, the first additions as a rule are followed by slowing, to the extent may be of doubling the length of the intervals, with scarcely any effect on the height of the beats ; a little later on, and with almost unchanged rhythm, the beats may diminish by two thirds within the short space of seven beats.

Thus, then, even the same heart shows no quantitative relation that is constant between excitability and contractility.

One might multiply evidence in the same direction. Thus, quite suddenly a heart, beating at intervals of fifteen to twenty seconds, will start off at a rate five to ten times as fast, with little if any variation in height of beat. But sufficient has been said to prove that, whatever underlies these two manifestations, which are measured by *contraction rate* and *contraction height*, they may be separately influenced, and therefore so far are distinct.

Hence one may speak of a drug as acting on either *excitability* or *contractility*, and the results already given may be more briefly and clearly summed up as follows :

In the case of the drugs already examined, and probably in all cases, the action is not exclusively on either *excitability* or on *contractility* ; *both* are affected.

The degree, however, in which one or other suffers varies with different drugs. Thus, with regard to the salts of the three different bases, sodium, ammonium, potassium, the effect on excitability varies greatly; and, whilst potassium salts strongly affect excitability, sodium and ammonium salts affect excitability relatively but slightly. And thus, whilst with potassium salts it was the exception not to get permanent arrest of spontaneous beats before contractility was destroyed, with sodium and ammonium salts it was the exception when spontaneous beats did not continue up to the very end, and, moreover, with a final frequency little short, often in excess, of the original frequency.

Though there is this broad division into potassium salts on the one hand and ammonium and sodium salts on the other, the salts of ammonium and potassium form the extremes, those of sodium being intermediate, affecting as they do excitability rather more than ammonium. As to the action on contractility, the quantities of the drugs used constitute the measure of this action, since in each case the contractility was reduced to *nil*. On examining the table of quantities it will be seen that a very different relation now obtains. Potassium and ammonium come very close together, whilst sodium is widely separated. The two former are so near numerically that it would be unsafe to draw inferences from the differences in the actual numbers; in passing to sodium the highest estimate, in the case of the chloride, bromide, and iodide, would give the relation as one to ten, the sodium salts being one tenth as poisonous as those of ammonium and potassium.

Table of quantities.

Potassium hydrate						Quantity in grs.	
						. 1.35	
	CHLORIDE.		BROMIDE.		IODIDE.		
	Quantity in grs.		Quantity in grs.		Quantity in grs.	Relation of molecu- lar weights.	
Sodium .	29.77	...	51.7	...	84.24	...	58.5 : 103 : 150
Ammonium	2.93	...	3.7	...	6.3	...	53.5 : 98 : 145
Potassium	2.46	...	3.28	...	3.16	...	74.5 : 119 : 166

CITRATE.		Molecular weights having equal number of atoms of base.	
Sodium	. 16.66	...	357
Ammonium	. 3.3	...	339
Potassium	. 2.46	...	324

In the above the only column which perhaps requires explanation is that giving the relation of the molecular weights. The object of this was to see, if, taking a given base, any relation could be traced between the action of its salts as here tested and the molecular weights of the same salts.

There does appear to be some such relation in the case of the sodium salts of chlorine, bromine, and iodine. But this fails in the case of the ammonium and potassium salts, and so, the results obtained do not point in any one direction. Obviously, however, a very much larger number of experiments would be needed to arrive at any definite conclusions, positive or negative, on this point.

One must be careful not to take effect on contractility as the exclusive measure of poisonous action.

Arrest of the contractions rather should be taken to represent the poisonous action, and this we have seen may happen in two ways, by the action on *contractility*, and by the action on *excitability*. Hence though as to the first ammonium and potassium show but little difference, as to the latter they diverge widely, and potassium stands as by far the more powerful poison.

The recognition of the above has especial importance from a clinical standpoint, for, if we be dealing with the functions of an organ, the arrest of such functions concern us more immediately than the precise mode in which such arrest is effected. And if a drug threaten in two directions, the dosage must take both of these into account.

Accordingly, represented in descending order, we have :

Potassium salts, most poisonous, both *excitability* and *contractility* powerfully affected.

Ammonium salts, next in order, *contractility* suffers almost alone.

Sodium salts, least poisonous, *contractility* suffers chiefly, but *excitability* is more affected than in the case of ammonium salts.

Further, it must be remembered that sodium salts are not only least poisonous of the three, but are, indeed, very weak poisons as compared with both potassium and ammonium salts.

The iodides and bromides of potassium and ammonium are so largely used that the importance of the foregoing is apparent if no further conclusion than this be drawn:—*that, the action on one tissue being selected and all other conditions being kept as far as possible identical, if one drug prove itself more active than another, it is at least not improbable that this same drug will also prove itself more active under the more complex conditions presented by the organism as a whole.*

A very guarded conclusion is obviously the only one that can be drawn when one passes as here from simple to very complex conditions, but the above conclusion is surely warranted.

Hence these experiments would suggest the substitution of the bromides and iodides of sodium for those of ammonium and potassium, and the use of those of ammonium preferably to those of potassium; but the very wide gap separating sodium salts from both ammonium and potassium points especially to the use of the first, and the more so that, so far as clinical evidence goes, it is to the effect that, therapeutically, the salts of sodium and ammonium are as powerful as those of potassium.

In conclusion, one or two points may be touched upon. The very slight degree of poisonous action of the chloride, bromide, and iodide of sodium, was such that very large quantities of the drugs had to be added, so much so, that physical changes, such as osmosis, became probably important factors in the arrest of the heart. This, of course, would not affect the previous statements, but would rather

place still lower in the scale of poisonous action the above sodium salts, for clinically, the doses given would never even approach those here used, so that physical conditions would scarcely become factors in their therapeutic action.

These physical conditions may, however, account for the peculiar occurrence of piling up under the influence of continuous faradisation, which phenomenon was constant for the above sodium salts, and which Fig. VII illustrates.

It will be seen further on that with sodic citrate, of which salt considerably smaller quantities were used, this phenomenon did not appear.

Another point which touches a subject of very great importance may also be noticed. Looking over the results obtained, it will be seen that the chlorides, bromides, and iodides of potassium closely resemble each other in their action; the same is true of the ammonium salts. The sodium salts are best not considered here, since the physical elements introduced might obscure any such relation existing. The facts then to be put together are:—that salts resembling each other in having a common base resemble each other in their action.

The statement, that of a series of salts with the same base, the poisonous action is dependent on the base is not new, certainly with regard to potassium salts. These experiments, so far as they go, tend to confirm this statement, which, however, can scarcely represent the whole truth, for looking back at the table of quantities, it will be seen that the citrate of potash is as poisonous as the chloride, and rather more so than the iodide and bromide; it will be said, this is in direct opposition to clinical evidence.

It would be so, if one is to hold that the frog's heart as here used takes into account the whole action of the drug, but, if a salt do not act as a whole but individual elements composing it keep their identity, so far as action goes, then one must assume that one side or aspect of the drugs examined is here left out, and that the test is an imperfect one.

This again does not invalidate the conclusions drawn, for, given the bromide, say of three different bases, and that the basic element alone is taken account of, one must assume that the unaccounted-for bromine element being constant in all three, may, after the manner of all constants, be disregarded, and the salts be represented *relatively* in terms of their differences, *i.e.* of their bases.

THE CITRATE GROUP.

These organic salts were chosen in order to contrast them with the very definite group of the iodides, bromides, and chlorides amongst inorganic salts.

Citrates of soda, ammonia, and potash.

Of soda and potash the tribasic salts were employed, of ammonia the di-ammonic salt.

With reference to the quantities used, an important element is the water of crystallisation, which varies in the above three salts. Thus :

The molecule of tri-potassic citrate contains one molecule of water of crystallisation	$K_3C^6H_5O_7 + 1Aq.$	Mol. wt. = 324
That of tri-sodic citrate, 5.5 of water, the crystals having the composition .	$2Na_3C^6H_5O_7 + 11Aq.$	„ = (357) ₂
That of di-ammonic citrate, none .	$(NH_4)_2HC^6H_5O_7$	„ = 226

The quantity of ammonic citrate which would contain the same number of atoms of the radical ammonium as the sodium and potassium salts, *i.e.* three, would be represented by the number 339. So that approximately equal weights of all three salts would contain the same number of atoms of potassium, sodium, ammonium.

Tri-sodic citrate.—This salt affects frequency but slightly, and so long as the contractions are visible, rhythm is manifest.

One case out of the six was somewhat exceptional, here

the effect on frequency was much more marked in the way of slowing, though even here in the final stages there reappeared a faint waviness of the trace, indicating faint spontaneous contractions.

The effect of continuous faradisation was certainly not diminished, if anything, it was increased. Even after the beats had completely ceased or had been reduced to a minimum, complete tetanus, though of a low altitude, was obtained.

In no case was the piling up obtained, which the chlorides, bromides, and iodides of sodium showed, when continuous faradisation was applied after the heart had been arrested by the drug.

The stress, as a rule, fell early on contractility, the contractions growing feeble rather rapidly, whilst rhythm suffered but slightly. In four out of the six cases, and doubtfully in a fifth, a certain amount of recovery took place under the action of the drug, *i.e.* the beats after reduction to a certain point, increased again slightly in spite of continued addition of the drug. The recovery was not, however, of long duration.

The early and sudden action on the height of the trace is noteworthy, in five out of the six cases it was marked, so that by far the larger amount of the drug was spent in destroying the small residuum of contractility remaining after the above primary effect.

The quantities employed were :

I.—Dec. 31.	Temp. of room	8°.	Quantity	16 c.c.
II.— „ 31.	„	8·5°	„	14
III.—Jan. 2.	„	11°	„	12·5
IV.— „ 2.	„	12·5°	„	13
V.— „ 6.	„	17°	„	5
VI.— „ 6.	„	17°	„	5
				—
				65·5

Average 10·83 c.c. = 1·083 grms. = 16·66 grains.

Citrate of ammonia $(\text{NH}_4)_2\text{HC}^6\text{H}_5\text{O}_7$.—In all six experiments spontaneous beats occurred up to the very end,

i.e. so long as contractility remained. As to quickening or slowing no constant effect was produced, but in two, out of the six, an effect similar to that caused by potash obtained, viz., a rather sudden slowing of the rhythm, with no appreciable change in contractility. As was the case with soda, a certain amount of recovery occurred after the beat had been primarily reduced.

With respect to faradic excitability, here, as with the soda salt, there was certainly no diminution, at any rate so long as the height of the beats were of sufficient value to give definite results in this direction. If anything, the change was towards increase.

When the contractility had been destroyed by the drug and single stimuli were without influence, continuous faradisation was equally without effect, *i.e.* no piling up obtained.

In four out of the six cases there was distinct primary increase in height of beat, in one it was doubtful, in one the only effect was a broadening of the beat. The stage of increase was of but short duration. The recovery before mentioned occurred in four out of the six cases; it took place after reduction of the beat to a very small quantity, and was but very slight. The decline in the height of the beats was gradual in some, in others occurred rather rapidly.

Quantities :

I.—Dec. 30.	Temp. of room	10°.	Quantity	2·4 cc.
II.— „ 30.	„	10°	„	3·3
III.—Jan. 4.	„	15°	„	3
IV.— „ 4.	„	16°	„	4
V.— „ 5.	„	17°	„	3·9
VI.— „ 5.	„	18°	„	3·4
				—
				20·0

Average 3·3 c.c. = 0·33 grms. = 5·09 grains.

Citrate of potash.—The effect of this salt was primarily to slow the rhythm. This set in early, appearing as a rule after the first dose, though it often went on increasing with the first few doses. As a rule, this early effect was

without a corresponding effect on the height of the beat ; thus the rate might be reduced by one half with little noticeable effect on the height of the trace.

Complete inhibition did occur in five out of the six cases, but not till the beat had been greatly reduced, viz. to $\frac{1}{4}$ th, $\frac{1}{5}$ th ($\frac{1}{5}$ th— $\frac{1}{6}$ th), $\frac{1}{5}$ th, $\frac{1}{5}$ th respectively, of the original height of the beat. This effect, then, was much less prominent than was the case with the chlorides, bromides, and iodides of potassium. The primary slowing above noted did not go on increasing at the same rate, and as a rule a stage followed in which great reduction in height occurred with scarcely appreciable change of rhythm.

Faradic excitability was markedly diminished, and a current giving strong tetanus before addition of the drug, finally failed to give any, or indeed only an initial contraction.

When the heart had been arrested by the drug and single shocks caused no effect, continuous faradisation was equally without effect.

There was no primary increase in the height of the beat, but decline from the very commencement ; but whilst in the early stage the stress appeared to fall on rhythm—the decline in height being very slight—later on the effect on contractility became marked, the trace in some falling rapidly without corresponding effect on rhythm.

Quantities :

I.—Dec. 29.	Temp. of room 7°.	Quantity 0.9 c.c.
II.— „ 29.	„ 7.5°	„ 1.8
III.—Jan. 3.	„ 15°	„ 1.8
IV.— „ 3.	„ 16°	„ 0.9
V.— „ 7.	„ 14°	„ 2.5
VI.— „ 7.	„ 14°	„ 1.8
		—
		9.7

Average 1.6 c.c. = 0.16 gm. = 2.46 grains.

The results obtained from the citrate group may be thus summarised :

Sodium and ammonium salts affect *excitability* but slightly ; they arrest the heart by destroying *contractility*.

Both appear, if anything, to increase *faradic excitability*.

Specially it must be noted, that when the heart has been arrested by sodium citrate, continuous faradisation is without effect, *i.e.* no piling up obtains. And, further, that the sodium citrate is much more poisonous than the sodium salts of the chloride group.

With respect to ammonium citrate, note that a primary increase in the height and breadth of the trace is the rule.

Potassium citrate affects both *excitability* and *contractility*, but the effect on excitability is much less marked than is the case with the potassium salts of the chloride group; still, the effect was decided, especially in the end stages.

There is nothing special as to the action on contractility. Faradic excitability is diminished from the commencement.

Comparing these results with those of the chloride group, we note the agreement of the sodium and ammonium salts, in the slight effect on excitability, and in the mode in which they arrest the heart.

They contrast, however, in their effect on faradic excitability; thus, whilst the chloride group lessens, the citrates appear to increase this.

In respect of sodium citrate, the two points specially mentioned, *viz.* relatively small dose and absence of piling up go together, and are of importance in relation to the chloride group, since here we had large dosage, and in all cases the final mounting up of the trace under continuous faradisation. The citrate results are in conformity with the view that this mounting or piling up indicates physical change in the muscular tissue.

In addition to the agreement above noted in respect of the effect on excitability and contractility, the ammonium citrate agrees with the ammonium salts of the chloride group in its primary effect of increase in height and breadth of trace. The only point of contrast hence is in respect of faradic excitability.

The potassium citrate contrasts with the potassium salts of the chloride group in its much slighter action on *excita-*

bility. It is true complete inhibition did obtain in five out of the six cases, but the beat was greatly reduced before such occurred.

In its influence on faradic excitability, there is agreement with the chloride group.

The doses required to destroy contractility are for both the ammonium and potassium citrates about the same as required in the chloride group. This question of poisonous action has been discussed with reference to clinical experience.

In the case of the salts of potassium we have the most complete series. Thus we have examined the hydrate, the chloride, bromide, iodide, and the citrate.

Taking the hydrate as the starting point, we note here—

1st. The tendency to produce *persistent spasm*.

2nd. The tendency to produce *inhibition*.

3rd. The tendency to lessen *faradic excitability*.

Passing to the chloride group, we note that the tendency to produce persistent spasm has disappeared, that the action on spontaneous excitability is, however, still very marked, also that on faradic excitability.

Passing to the citrate of potassium, we note the absence of any tendency to produce persistent spasm, that the action on spontaneous excitability, *i.e.* the tendency to inhibit, is much diminished; that the action on faradic excitability still remains, though it is difficult to state comparatively the degree in which it persists.

With the exception, then, of the persistent spasm feature, we note a similarity in the nature of the action running through all these salts of potassium.

The ammonium series is less complete since the influence of the hydrate on the spontaneous working of the heart could not be so completely tested.

Here we note, however, that the tendency to produce persistent spasm runs through all the salts of ammonium; though in the chloride group and in the case of the citrate, this tendency is but slight, appearing early and for only a short period.

Further, amongst the salts of ammonium there is agreement in the negative quality of slight action on rhythm.

As to the effect on faradic excitability there is no agreement, for whilst ammonia increased the above the iodide lessened it, whilst the citrate increased it. (The chloride and bromide were not examined.)

The sodium salts can be less easily compared, for in the chloride group, physical action probably comes into play. The persistent spasm which the hydrate excites does not appear with any of the salts. The action on spontaneous excitability is slight as compared with potash salts, and in this respect there is agreement throughout the sodium salts. The action is, however, more marked than in the case of ammonium salts. As to the effect on faradic excitability, the sodium salts show as little constancy of action as those of ammonium; thus, whilst soda increases faradic excitability the iodide lessens it, whilst the citrate shows, if anything, a tendency towards increase.

EXPLANATION OF DIAGRAMS.

DIAGRAM 1.

FIG. I.—Illustrating “genesis of tetanus” by fusion of beats, the result of continuous faradisation.

A, B, C, show the effect of increasing the strength of the current, the frequency of interruption of the primary current remaining the same.

The figures above the lines represent the positions of the secondary coil.

D, represents a later stage.

As the strength increases from 7·5—7—6, it will be seen that the more complete tetanus also corresponds with the greater number of contractions. In D the fusion is so complete that individual beats are no longer countable.

FIG. II.—Shows effect of sodium hydrate on the excitability of the ventricle to continuous faradisation.

Nov. 25. Temperature of room 16° C.

- A. Before the addition of sodic hydrate.
- B. After 25 minims of a 1 per-cent. solution.
- C. After 75 ,, ,, ,,

FIG. III.—Shows similarly the effect of ammonium hydrate.

Nov. 26. Temperature of room 15.5° C.

- A. Before the addition of ammonium hydrate.
 - B. After the addition of 10 minims of 1 per-cent. solution.
 - C. ,, ,, 24 ,,
 - D. ,, ,, 55 ,,
- } see Diagram 2.

Fifty-six minutes from first dose.

DIAGRAM 2.

FIG. III, A. and B. (see above).

FIG. IV.—Shows effect of potassium hydrate. A 10 per-cent. solution was here used.

Feb. 12. Temperature of room 16° C.

- A. Before addition.
- B. 10 minutes later after 0.15 c.c. = 2.55 minims. The tetanus is here taken in the earliest stage of the potash effect, note the faint evidence of diastolic rise.
- C. 10 minutes from B, after 6 minims in all. Note the diminution of effect, together with the presence of considerable amount of persistent spasm.
- D. and E. are after 7.6 minims and 9.3 minims respectively, they show progressive decrease in excitability.

FIG. V.—Jan. 28. Temperature, 16.5° C. Bromide of ammonium, 10 per-cent. Chosen as typical of the action of ammonium salts of this group, viz. chlorides, bromides, iodides.

- A. Shows effect of first addition of 0.2 c.c. = 3.4 minims also a few beats before the addition.
- B. About five minutes from first addition; 0.6 c.c. = 10 minims have been added.
- C. 10 minutes from B, 1.8 c.c. = 30.5 minims have been added.
- D. 2 minutes from C, 2.2 c.c. = 37.3 minims ,,

DIAGRAM 3.

E. Comes immediately after D, 2.4 c.c. = 40.6 minims was the total quantity added.

Note certain amount of persistent spasm in A and B, the beats are too frequent for diastolic contraction to appear between the individual contractions.

Note slight irregularity preceding the end stage.

FIG. VI.—Jan. 19. Temperature 15° C. Bromide of potassium, 10 per cent.

A. First dose 0.1 c.c. = 1.7 minims.

B. 4—5 minutes later, after 0.3 c.c. = 5.07 minims

C. 2—3 minutes later, fifth dose = 0.5 c.c. = 8.45 minims

D. 3 minutes later. The last spontaneous beat is here represented, viz. after 0.8 c.c. = 13.52 minims, so that hence on there was complete inhibition.

E. 10 minutes later, 1.1 c.c. and 1.2 c.c. (18.6 and 20.3 minims) = the quantities added. The beats are the result of excitation.

F. 8—9 minutes later, after 1.4 c.c. = 23.7 minims.

G. 5 minutes later, final stage, 1.7 c.c. = 28.8 minims, the total quantity added.

Note the primary slowing in B and C, the rhythm was further somewhat irregular; in D, just before complete inhibition, there was considerable irregularity. The subsequent charts show that, though inhibited, contractility still remained, the figures above the beats represent the positions of the secondary coil.

FIG. VII.—Showing effect of continuous faradisation after heart has been arrested by bromide of sodium. The charts are typical of the chlorides, bromides, and iodides alone.

A. Jan. 24. Temperature 17.5° C. Sodium bromide 10 per cent. The effect of continuous faradisation with the secondary coil at 4, and at 0 (pushed home) is shown. The previous want of effect of single shocks is shown, and of continuous faradisation at 6.

B. Jan. 27. Temperature 17° C. Sodium bromide 10 per cent.

Similar to above, this perhaps represents the more usual degree of effect produced.

Diagram I.

Fig: I.

A.

"

C

"

D

Fig: II.

B

Fig: III.

C

Fig: III.

D

7

7.5

6

3

5

7

7

7

6

6

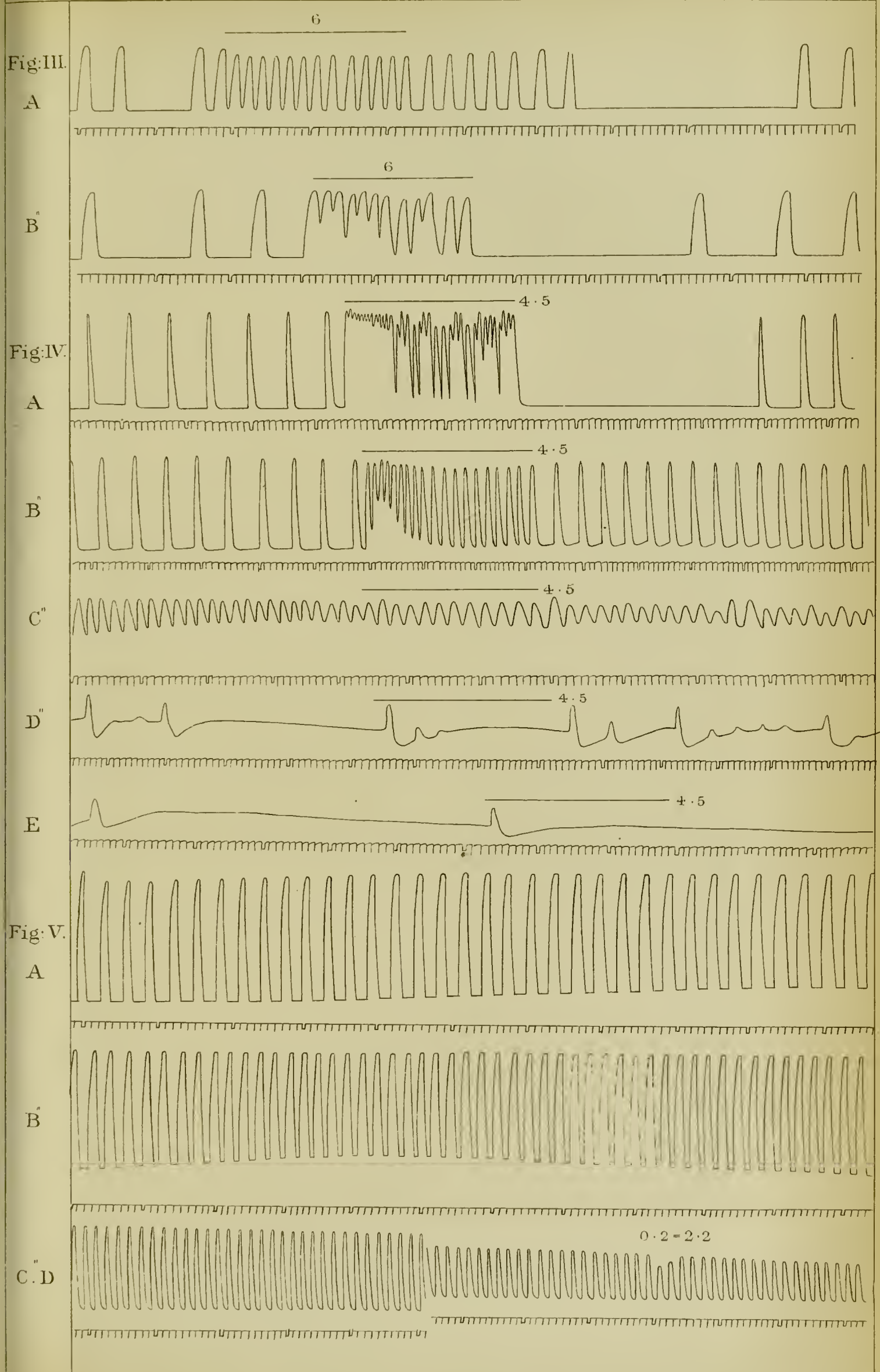


Fig. V.
E.

0.2 = 2.6

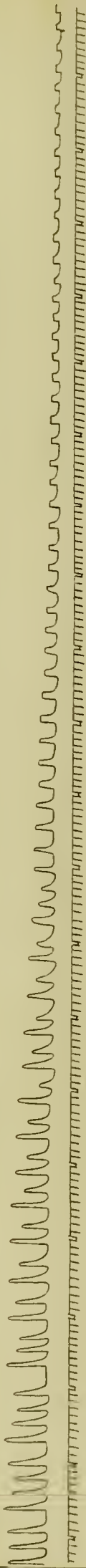


Fig. VI.
A. B.

0.1

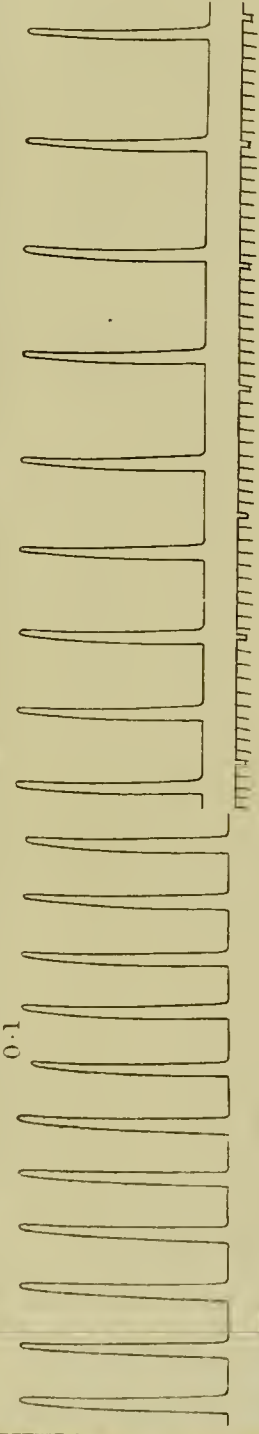
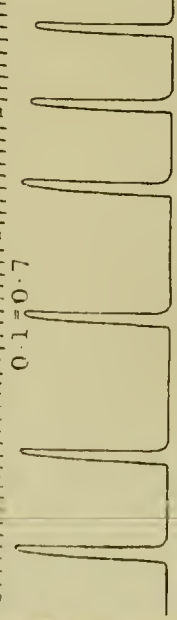


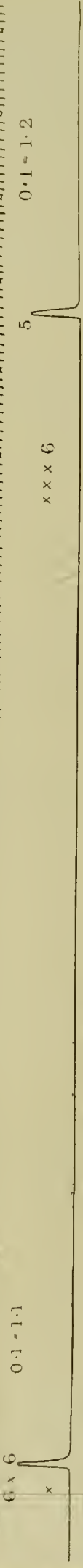
Fig. VI.
D.

0.1 = 0.7



E.

6 x 6



F.

0.1 = 1.1

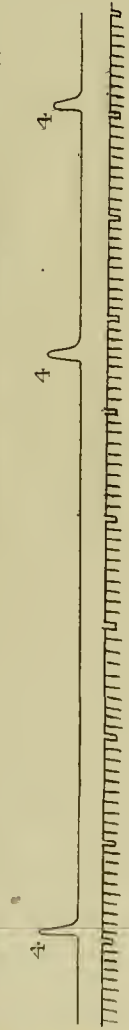


Fig. VII.
A.

4

4

0.1 = 1.7

4

4

0

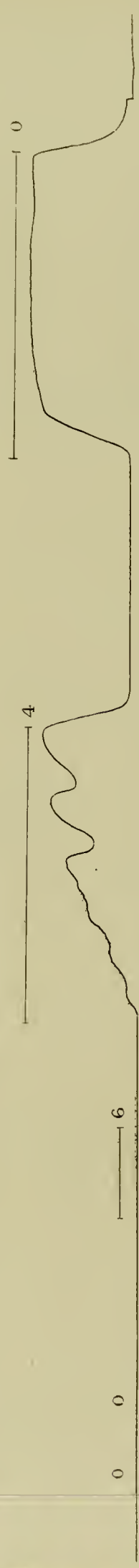


Fig. VII.
B.

2

0

5

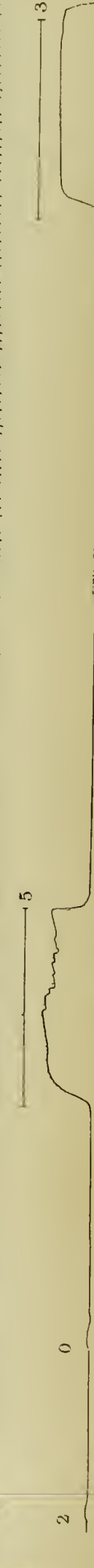


Fig. V.
E.

Fig. VI.
C.

Fig. VI.
G.

INVESTIGATIONS
INTO THE
ACTION OF THE DIGITALIS GROUP.

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Read November 21st, 1883.

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THE influence of digitalis on the circulation is, of course, the principal feature in the action of this drug. The primary slowing and increased vigour of contraction of the ventricle, the subsequent stage of irregular action as the dose is increased, and the final arrest of the ventricle in full systole are all well-known facts. To these must be added, rise in blood-pressure, an effect occurring uniformly, and which some authors consider of chief importance; certain, at least, of the cardiac effects of digitalis being, according to these, secondary to the increased blood-pressure. In a recent paper on the subject,¹

¹ "Beiträge zur Kenntniss der pharmakologischen Gruppe des Digitalins," 'Archiv f. experimentelle Pathologie u. Pharmakologie,' Bd. xvi, p. 149.

Schmiedeberg thus classes the blood-pressure effects in relation to the cardiac effects :

1. Rise in blood-pressure accompanied, as a rule, but not necessarily, by slowed pulse rate.

2. Continuance of increased blood-pressure, with increased pulse frequency.

3. Continuance of raised blood-pressure with great irregularity in the heart's action.

4. Rapid fall in blood-pressure, stoppage of the heart ; death.

Schmiedeberg attributes the therapeutic value of digitalis alone to this rise in blood-pressure ; the slowing of the pulse, which is usually witnessed, he holds to be secondary to the rise in blood-pressure, a reflex on the heart through the vagi ; the rise in blood-pressure itself, however, he makes dependent on the heart's action, and he further states that it is not attended by diminution in the calibre of the vessels. To a consideration of the relation between the heart's action and blood-pressure rise we shall return later on. What now concerns us rather is the condition of the heart and that of the arterioles. Concerning the former there is no difference of opinion, the ventricle is admittedly arrested in systole ; concerning the latter the balance of evidence certainly appears to show that the arterioles contract under the influence of digitalis,¹ though Schmiedeberg, as above stated, denies this. But, allowing even that digitalis does cause the arterioles to contract, the question still remains, how does it do so ? On the heart the action is generally admitted to be direct, but on the vessels it is held by most to be indirect, by the stimulation, viz. of the vaso-motor centres at the base of the brain. Ackermann almost alone maintaining that the action on the arterioles is direct (Wood, *op. cit.* p. 139).

The question is clearly one of considerable importance, and it bears directly on the definition of the digitalis action. Schmiedeberg, in the before-mentioned paper, enumerates a long list of bodies resembling digitalis in

¹ ' Consult Wood, ' Treatise on Therapeutics,' 3rd edit., pp. 138-139.

their action, and which he classes as digitalis remedies. The definition of such action being the primarily increased vigour of the ventricular contraction leading up finally to the systolic arrest, together with the blood-pressure rise. The question now, rather, is what is essential in this action, and whether we may not take as such the spasmodic condition of the heart, and accordingly define digitalis action as—*the production of continuous spasm of the heart muscle by direct action of the drug on this tissue*: this spasm not being of the nature of tetanus, *i. e.* of fusion of adjacent beats, and following on the application of the drug, either to the whole heart or to any limited portion of the ventricle, in the latter case causing a local spasm. Thus defined, Schmiedeberg's already very large group will have to be extended and made to include, among others, the caustic alkalies and barium chloride, acetate and nitrate,¹ and very probably many others.

Taking this as the definition of digitalis action, is it not probable that a drug thus directly acting on the muscular tissue of the heart will likewise affect directly the muscular tissue of the arterioles? Indeed, is one not justified in assuming that the likelihood of similar action of one drug on two or more tissues will be in proportion to the resemblance existing between these, approaching certainty as the tissues increasingly resemble each other, becoming less probable as they diverge? If this be allowed, the inference is not far from the heart to the arterioles, and given a particular action on the one, we should look for similar action on the other, and hence we should expect to find the digitalis (spasmodic) heart accompanied by spasm of the arterioles. This is, of course, on the assumption that the muscular elements of the arterioles may be influenced directly by the fluids bathing them. For the argument in evidence of this we must refer to Gaskell's paper on the tonicity of the heart and blood-vessels.²

¹ Boehm, "Ueber die Wirkungen der Barytsalze auf den Thierkörper," 'Archiv f. Exp. Pathologie und Pharmak,' 1875, iii, pp. 216, *et seq.* Also paper by the writers, 'Brit. Med. Journ.,' Aug. 11, 1883.

Journ. of Physiology, vol. iii, p. 48.

Whilst bearing in mind the resemblances existing between the muscular elements of the heart and arterioles, it is necessary that we do not lose sight of their differences. These differences are not merely structural, for functionally, whilst the muscular fibres of the heart and arteries resemble each other broadly, in that they are both forms of tissue specialised for the function of contracting, they differ widely in the mode in which they manifest this property. Contractility in the fully-differentiated organism, we find manifested after two modes, viz. after a slow persistent fashion and after a sudden explosive fashion. Non-striated and striated muscular tissues represent structurally the two extremes of this functional difference. The slow persistent contraction above named is closely allied, if not identical, with that condition we name *tonus*, which is specially characteristic of unstriped muscle. In striped muscular tissue, though the sudden contraction is the most striking characteristic, yet the slow persistent form is also present, and we speak of *tonus* for these muscles also. The heart muscle, according to physiologists, is intermediate functionally between the striped and the unstriped tissue; its contractions are more sudden than those of the latter, less sudden than those of the former. At the same time *tonus* is a marked feature of cardiac muscle. Concerning the element rhythm, which is characteristic of plain muscular fibre, and also to a marked degree of the heart, we do not find this intermediate position maintained.

Arguing, then, from this intermediate position of the heart with its affinities manifested in the two directions of the voluntary and involuntary muscles, we would suggest that it may be possible, from action on the heart, to infer in both of these directions; *e.g.* supposing that we find that the stress of action of a drug, applied to the excised heart, show itself mainly as affecting the character of the beat itself, we should then be led to infer that the drug will strongly affect voluntary muscular fibre, whilst, on the other hand, should it powerfully affect the tone of the heart, either in the way of increase or diminution, we should

then conclude that it will similarly affect the arterioles. It is essential to remember here that we are dealing with the excised heart, and hence are inferring from the local action on this tissue to the local action on other tissues.

We have made the above suggestion as to the possibility of inference from the heart to the voluntary muscles; the object, however, which we had principally in view was to establish experimentally the inference from the heart to the arterioles; and, accordingly, taking for our starting point the systolic heart of the digitalis group, we proceeded to examine the direct action of the members of this group on the vessels themselves.

Mode of experimentation.—This was the same as that adopted by Gaskell in his experiments on the direct action of acids and alkalies on the tonicity of the vessels (op. cit.), but here, as in our previous experiments with barium chloride, the tortoise was used instead of the frog. The exact method was as follows:—The animal was pithed, care being taken to destroy as completely as possible the spinal cord, the shell sawn through transversely and the soft parts divided. A cannula was then tied into the abdominal aorta distally, the hinder half of the body alone being used in the experiment. The cannula was fed with the required fluids by simple syphon action, and the flow accordingly was into the abdominal aorta and out through the cut abdominal veins. In order to measure the rate of flow, the preparation was placed on a tilted glass plate from which the escaping fluid drained into a graduated glass measure, by which means we were enabled to read off the amount of outflow for any given interval of time.

The pressure employed varied slightly in the different experiments, averaging about 30 centimetres, but, during each experiment it was maintained constant within 0·5 centimetre by continuous additions to the supply vessel, which was of large capacity, so as to retard changes in level.

The experiments were performed in May, June, and July of 1883. Each experiment lasted some considerable

time, two to three hours or even more, and inasmuch as the circulation of artificial saline fluids continued over lengthened intervals of time tends to produce œdema of the tissues, which œdema may even occasion considerable obstruction to the circulation,¹ it became necessary to try the effect of the circulation of the unpoisoned saline, over periods which would cover the duration of an ordinary experiment. By this means it was possible to see if the amount of *ischæmia* witnessed after the administration of a drug could be accounted for on the grounds of œdema alone.

Another point remained for consideration, viz. the vitality of the tissues. In the case, for instance, of a negative result, *i.e.* the addition of the drug to the circulating fluid remaining without effect on the rate of flow, the question arose whether the tissues were still vital and the arterioles still capable of contracting; this question was the more important the longer the experiment had lasted. We must here forestall the evidence as to the action of digitalis, and state that this drug acts most unequivocally and most strongly in causing the arterioles to contract, and that the effect comes out so rapidly that it is quite impossible it could be other than a vital effect. Hence, in this drug we had a means of determining the vitality of the tissues, for if at the end of an experiment, and after continued additions of the drug, the flow still remained unobstructed—the addition of digitalis to the circulation would at once determine whether the arterioles were still able to contract and so obstruct the flow. In the case of negative results, accordingly, this plan was adopted.

Two experiments were performed with *simple saline*,²

¹ See experiments by Glax and Klemensiewicz, 'Sitzungsberichte d. Akademie zu Wien,' vol. lxxxiv, Abth. iii, p. 216.

² The saline employed was a solution of 0·6 per cent. of sodium chloride in tap water. It is necessary to make this statement, since the small quantities of salts contained in ordinary tap water appear to exert important effects and make the distinction between such saline and that made with distilled water

we will quote the one showing the greatest variation in the rate of flow.

June 18th.—Temperature of room 17° C.; head of pressure 31 centimetres.

The following numbers were observed: outflow per five minutes in cub. cents. 80, 85, 95, 82, 88, 83, 78, 75, 70, 60, 68, 66, 65, 65, 65, 77, 79, 78, 80, 80, 77, 80, 83, 80, 82, 86, 79, 84, 83, 86, 80, 80, 84, 81, 79, 83,¹ 35, 15.

¹ Digitaline solution, 1 per cent., 1 c.c. added to the 200 c.c. of saline.

The second experiment showed a considerably more uniform rate of flow than that here seen; but the important point to note in the above experiment is that at the end of three hours the rate of flow is undiminished, and that at this time the vitality of the tissues is still maintained, as is manifest by their immediate reaction to digitaline, the flow lessening at once from 83 c.c. to 35 c.c. in the next interval of five minutes, and thence to 15 c.c. Exactly similar results obtained for the second experiment, the rate of flow at the end of three hours was at the highest figure recorded during the experiment, and from this, viz. 48 c.c. it fell, on the addition of digitaline, at once to 25 c.c., and in the five minutes following this to 4 c.c.

Digitaline.—The digitaline employed was obtained from Morson. The above two experiments both show the effect of digitalis in obstructing the circulation and the rapidity with which this is effected. Of three other experiments, made simply with a view to test the action of digitaline, the results were in each case similar. We will quote only one.

May 24th.—Temperature of room 24° C.; head of pressure 31 centimetres.

Outflow per five minutes in c.c.—90,² 88, 80, 84,³ 48,

² Saline solution, 0.6 per cent. supplied. ³ Digitaline, 1 per cent., 0.5 c.c. added to the 100 c.c. saline.

a very essential one, *vide* Ringer, "On the influence exerted by the Constituents of the Blood on the Contraction of the Ventricle."—'Journal of Physiology,' vols. iii and iv,

28, 12,¹ 6, 9, 17, 24, 31, 34,² 25, 10, 4,³ 2, 2, 2, —, —, 11.

¹ Saline substituted. ² Digitaline saline again supplied. ³ Saline again substituted.

The evidence of the other experiments was precisely to the same effect, and they are omitted simply on account of space. In the above experiment the alternation of effect is to be observed, *e.g.* with the supply of the digitalis saline the rate of flow at once begins to fall rapidly, on resubstituting pure saline it slowly begins to rise.

It is to be noted that the minimum is, in the above, reached after the replacement of the poisoned circulation by saline, this of course simply means that the digitaline had not had full effect and that the process of washing it out was not an immediate one. The blank spaces in the last section simply represent four intervals of five minutes allowed to elapse before again measuring the rate of flow, the last figure shows this to have been slowly increasing.

Barium chloride.—For the details of the experiments with this drug we must refer to our paper in the ‘Brit. Med. Journ.’ for August 11th, 1883. The method adopted in these experiments was precisely the same and the results equally unequivocal. *Barium chloride acts strongly and directly on the small arterioles, causing these to contract.* It may be remembered that Boehm⁴ had previously demonstrated the digitalis-like action of the salts of this base in the production, viz., of the retarded pulse-rate, the heightened blood-pressure, and the systolic heart.

Strophanthus (the African arrow poison, *Strophanthus kombi*).—Two experiments were made with this drug. A 5 per cent. solution of the crude drug was employed. The results were much less striking than for digitaline, still they were in the same direction as for this latter. We will quote one experiment.

“Ueber die Wirkungen der Barytsalze auf den Thierkörper,” ‘Archiv für experimentelle Pathologie u. Pharmakologie,’ 1875, iii, pp. 216, 251.

May 28th.—Temperature of room 20° C.; pressure 31 centimetres.

Rate of outflow per five minutes in c.c.—42,¹ 39, 41, 41,² 37, 28, 25, 27,³ 23, 24, 22, 18, 16, 10, 10, 11, 11, 12, 15, 16, 18, 20,⁴ 20, 11, 9, 10, 9, 10, 10, 8, 9, 7.

¹ Saline solution, 0·6 per cent. supplied. ² Strophanthus 5 per cent., 0·4 c.c. to 100 c.c. saline. ³ Saline solution replaced. ⁴ Strophanthus 5 per cent., 1 c.c. to 100 c.c. saline.

It is to be noted that in this experiment, though the effect of the strophanthus is much less sudden and much less marked, yet that, following the addition of the strophanthus, there is a steady unbroken fall, continuing it is true long after the replacement by saline, but again re-appearing after the rate of flow had begun to mount, on the readdition of strophanthus.

The second experiment gave a very sudden fall of the rate of flow following the first addition of strophanthus; throughout the remainder of the experiment the rate of flow, during the periods of saline substitution, never rose to within one half the initial rate of flow, and on this lowered rate the subsequent additions of strophanthus gave no decided effect in further reducing it.

*Scillitine.*⁵—Two experiments with a one per-cent. solution were made but the results were not decided, and they scarcely permit of more than the negative conclusion that the action if of the same kind as that of digitalis, comes very far indeed behind it in degree. Large doses were

⁵ We are indebted to Mr. A. W. Gerrard, F.C.S., Lecturer on Pharmacy at University College Hospital, for the following account of his method of preparation of the scillitine employed in our experiments: "Five pounds of squill bulb were exhausted with proof-spirit, and the resulting tincture treated with four times its volume of 84 per cent. alcohol; this caused the precipitation of a viscous, tenacious extract, the spirit retaining in solution the scillitine. The alcohol was removed by distillation and the residue treated a second time with alcohol and the alcohol again distilled off. A pale green extract was thus obtained which was washed with ether to separate the green substance, and further diluted with water to precipitate resin and colouring matter. The clear aqueous solution was now evaporated and gave a pale scaly mass of scillitine, answering to the reactions of a glucoside."

employed, viz. as much as 5 c.c. of the one per-cent. solution to the 100 c.c., and the contrast between the comparatively slight action of this substance and the very striking and sudden effect produced by the digitalis in one fifth the dose, was very marked. The digitalis was tried in the end stages of both of the scillitine experiments, and the rate of flow fell almost at once to a minimum, which practically amounted to complete obstruction.

Dyak poison.—This is an arrow poison used by the inhabitants of Borneo, concerning the origin of which nothing certain is known, but it contains in all probability the juice of *Antiaris toxicaria* as a chief constituent.¹ It is a heart poison and acts in this respect like digitalis. Two experiments were made with this substance, we will quote one of these which, in addition to illustrating the influence of the dyak poison, shows well the relative action of digitaline. The solution strength was a one per-cent. of the crude drug.

June 15th.—Temperature of room 19° C.; head of pressure 31 centimetres.

Rate of outflow per five minutes in c.c.—72,² 74, 76, 71,³ 70, 63, 55, 48, 39, 37, 37, 36, 32, 36, 36,⁴ 36, 42, 40, 44, 46, 46, 46, 48,⁵ 47, 47, 47, 46, 45, 45, 47, 48, 44,⁶ 43, 43, 40, 40, 36, 36,⁷ 24, 4.

² Saline solution, 0.6 per cent. supplied. ³ Dyak poison 1 per cent.; 0.5 c.c. to 100 c.c. saline. ⁴ Saline solution resubstituted. ⁵ Dyak poison 1 per cent.; 1 c.c. to 100 c.c. saline. ⁶ Dyak poison 1 per cent.; 4 c.c. to 100 c.c. saline. ⁷ Digitaline 1 per cent.; 1 c.c. to 100 c.c. saline.

This experiment shows in the first instance a decided fall on the administration of the poison, from this fall the recovery with the saline is but slight, but the further addition of the poison remains practically without effect, though in the last instance the dosage is increased considerably. The last two figures show well the powerful relative effect of digitaline and they further demonstrate the persistence of vitality in the tissues after over three

See Husemann, 'Vergiftungen,' p. 482 (Maschka's 'Handbuch d. Gerichtlichen Medicin,' vol. ii).

hours of artificial circulation. The second experiment gave results more decided in favour of the dyak poison, both the first and the second additions of the poison reducing the rate of flow by one half; still it places this poison far behind digitaline in its direct action on the vessels.

Convallamarin.—This is a glucoside obtained from *Convallaria majalis* and is classed among digitalis remedies¹. But one experiment was made with this substance; we quote it as follows:

June 21st.—Temperature 17·5°; head of pressure 31 centimetres.

Rate of outflow per five minutes in c.c.—22,² 22, 24, 29, 33,³ 23, 22, 24, 19, 16, 16, 16, 18,⁴ 18, 22, 25, 26, 29, 30, 33,⁵ 29, 24, 20, 17, 16, 15, 17,⁶ 15, 17, 17, 16, 16, 16,⁷ 16, 3, 1.

² Saline solution, 0·6 per cent. supplied. ³ Convallamarin 1 per cent.; 0·4 c.c. to 100 c.c. saline. ⁴ Saline solution replaced. ⁵ Convallamarin 1 per cent.; 0·8 c.c. to 100 cc. saline. ⁶ Saline solution replaced. ⁷ Digitaline 1 per cent.; 1 c.c. to 100 c.c. saline.

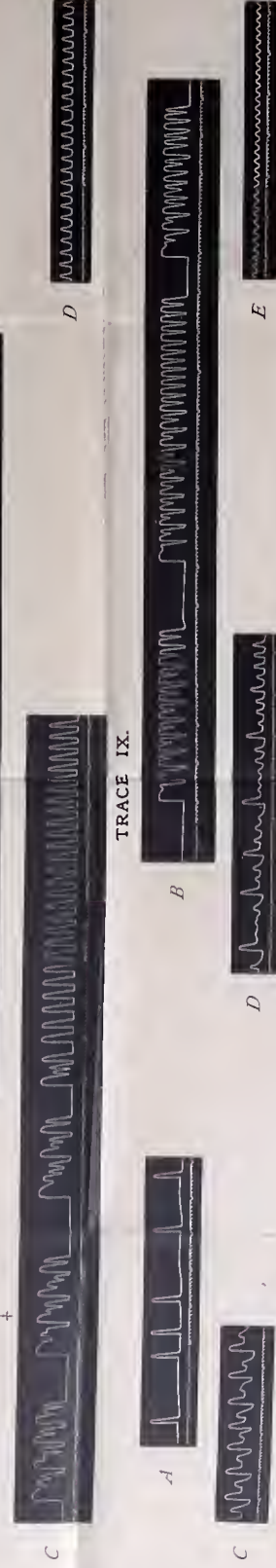
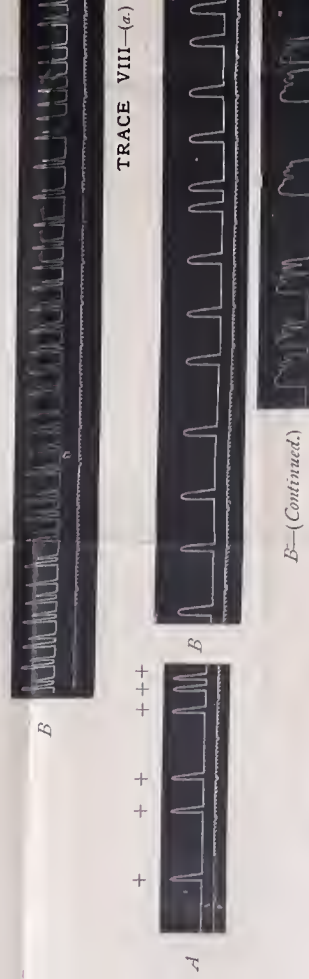
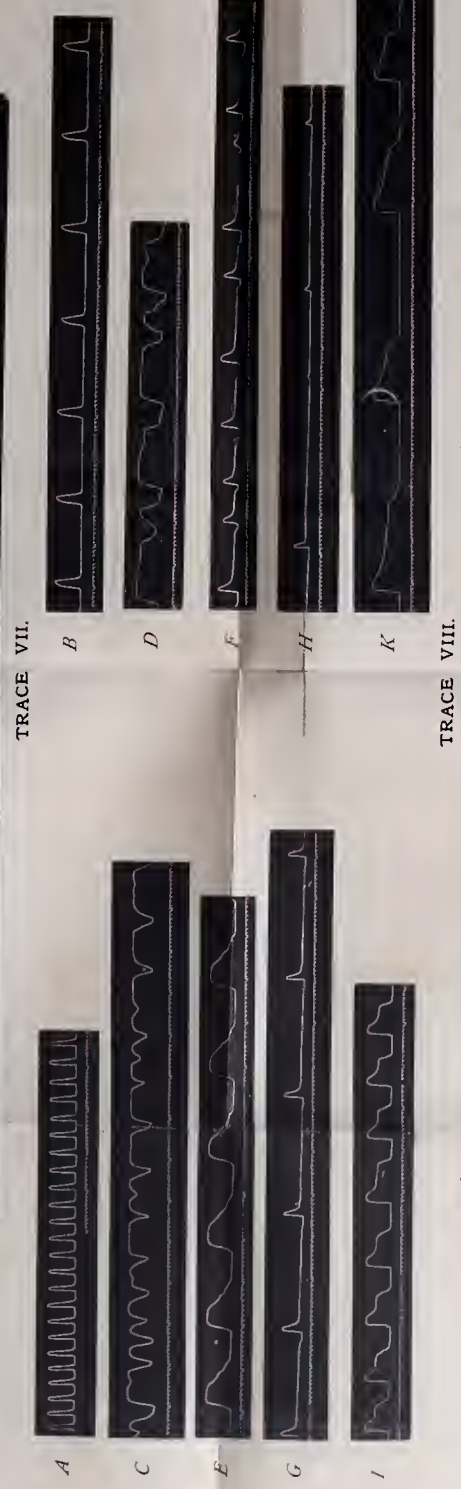
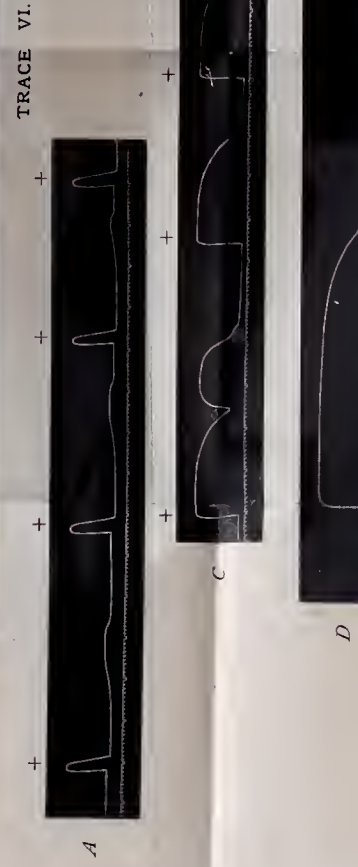
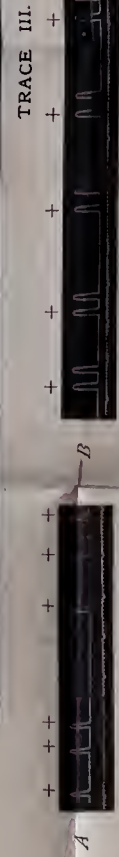
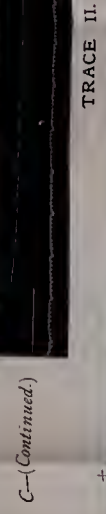
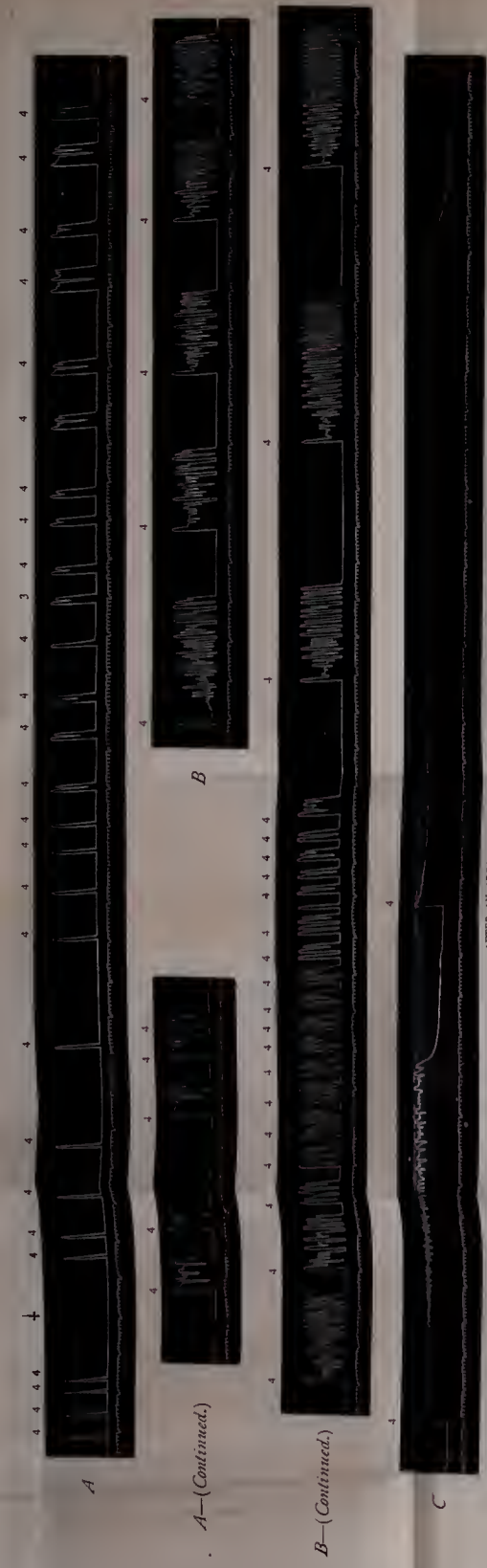
The results are not very striking, but it will be observed that the first addition of convallamarin reduced the rate by almost one half, viz. from 33 c.c. to 18 c.c.; that saline replacement brings back the previous rate of flow 33, and that convallamarin again reduces this rate by one half; the subsequent addition of saline does not show recovery. The last three figures show the immediate and marked effect of digitaline.

It will be remembered that Gaskell (op. cit.) demonstrated the effect of alkalies on the arterioles of the frog,

¹ Mr. Gerrard kindly prepared this substance for us and as follows: "The plant was exhausted with rectified spirit and the spirit distilled off; the residual extract was dissolved in water and evaporated to a thick fluid, then treated with ten times its volume of alcohol, filtered, and evaporated. The residue was now treated with tannin in excess, to form tannate of convallamarin, which after purifying by washing with alcohol was rubbed up with a little water and lead oxide—tannate of lead and free convallamarin being the result; the latter was removed by alcohol and obtained as a straw-coloured scale on evaporation."

this effect being constriction even to the extent of complete obstruction in some cases. The reverse obtained for acids, *i.e.* the vessels dilating under the influence of the acid. Dr. Gaskell employed solutions of sodium hydrate and of lactic acid to demonstrate these effects. We have repeated these experiments on the tortoise for the following alkaline salts ; potassium hydrate, carbonate and bicarbonate, sodium carbonate and bicarbonate. The potassium salts gave us like results as also did the sodium carbonate ; in all cases the vessels became constricted. With the sodium bicarbonate, however, we did not get this result, the flow instead of diminishing in rate appeared, if anything, to actually increase. This result, moreover, was obtained although the sodium bicarbonate was employed in such doses as to produce a deeper blue with test-paper than did the sodium carbonate. What this may mean exactly it is difficult to say, but if the ability to turn red litmus paper blue be accepted as the definition of alkalinity then an exception must be made in favour of sodium bicarbonate in respect of the statement that alkaline salts increase vascular tone. The power of a salt to saturate an acid obviously cannot be taken as a measure of its alkalinity since a molecule of sodium hydrate and of sodium bicarbonate would for all the stronger acids show an equal capacity in this respect, yet the latter is a comparatively saturated salt as contrasted with the former. We have laid the greater stress on this point because Gaskell has drawn attention to the acid and alkaline effects as rather fundamental differences and has suggested that all bodies may show a general division into acid-, and alkali-like actions ; thus he suggests that antiarin and digitaline would come under the latter heading, muscarin under the former. However, with this exception of sodium bicarbonate the results obtained on the tortoise with the remaining alkaline salts confirm those obtained by Gaskell on the frog.

Simultaneously with these experiments on the vessels others were made on the excised frog-heart. In these an





CONCERNING THE ACTION
OF
SALTS OF POTASH, SODA, AND AMMONIA
ON THE
FROG'S HEART.

BY
SYDNEY RINGER, M.D., F.R.C.P.,
PROFESSOR OF MEDICINE AT UNIVERSITY COLLEGE, LONDON,
AND
HARRINGTON SAINSBURY, M.D., M.R.C.P.

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CAUSTIC POTASH, soda, and ammonia, also certain of the salts of potassium, sodium, and ammonium, were examined as to their action on the frog's heart, and found to affect this differently. A word of explanation as to the plan of the paper will be of service.

The mode of experimentation, and the results obtained with the hydrates and with the iodides, bromides, and chlorides of the above bases are first given. These results are then discussed, and the conclusions drawn. Finally, experiments with the citrates of potassium, sodium, and ammonium are given, and the results contrasted with those obtained with the previous salts.

The object in thus separating the salts was that the chlorides, bromides, and iodides might the better be considered apart from the rest as forming a group by themselves. In the table of quantities this plan has been departed from, the citrates being classed with the above salts; this is for the convenience of comparison and to avoid repetition.

The mode of experimentation was the following:—A Roy's tonometer was employed, the heart was tied on to the cannula as near as possible to, if not in, the auriculo-ventricular groove. (It is not always possible to avoid having a portion of the auricle below the ligature; this will be referred to later on when the experiments are discussed.)

As in previous experiments dried bullock's blood dissolved in water, so as to represent normal blood, was used; this was diluted in the earlier experiments with 2 parts of saline solution, $\frac{3}{4}$ per cent., in the later experiments with $2\frac{1}{2}$ parts. In the former 3 oz., in the latter about $3\frac{1}{2}$ oz. (more exactly 100 cubic centimètres), of this mixture were taken.

Where the action of the drugs was estimated quantitatively the dose was as far as possible kept uniform, and the times of addition also, the dose in question being added every quarter revolution of the cylinder (about $2-2\frac{1}{2}$ minutes) to the whole mass of circulating fluid. The duration of each experiment was made as near an hour as possible, in order to reduce the error due to natural exhaustion which over lengthened periods would become considerable. The dose in consequence had to be adapted to this period. The tracings read from left to right.

The experiments were made in November, December, 1881, January and the early part of February, 1882.

The drugs were tested in two directions:

1. As to their action on the spontaneous working of the heart.

2. As to their action in modifying the effect of continuous faradisation applied to the heart.

The latter action will be first described, and this requires that the effect of continuous faradisation should be described.

Continued faradisation, provided the strength of the current be sufficient, and the interruptions frequent enough, causes in the normal heart a condition of continuous contraction, *i.e.* spasm, of greater or less extent.

To this persistent spasm—in which *fusion* of rhythmic contractions is the most obvious factor—the term “Tetanus” is here applied. As such it resembles closely the tetanus of a skeletal muscle, though differing in certain points.

Marey (‘*Physiologie experimentale*,’ vol. ii, p. 81, 1876¹) we believe was one of the first to describe tetanus of the heart. He shows that the excitability of the heart is not the same at different moments of a cardiac cycle; thus a minimal stimulation administered during systole will not cause a contraction; the period during which this obtains is called the “refractory phase.” The length of this period varies with the strength of the stimulus; the stronger the stimulus the less the duration, till the refractory phase quite disappears. Hence, when a series of *weak* electrical stimuli act on the heart, the greater number occurring during the refractory periods are ineffectual, and the number of systoles is much less than the number of excitations. But if the intensity of the current be increased (the frequency of interruption being unchanged), the refractory period lessening, the number of systoles approaches that of the excitations, and may equal them, a fusion results, *i.e.* a condition of tetanus.

Besides the influence of strength of the stimulus, Marey further shows that whilst cold increases heat diminishes the refractory period.

In our experiments, where continuous faradisation was

¹ Luciani (‘*Ludwig's Arbeiten*,’ 1872) had previously drawn attention to persistent spasm—the result of fusion of neighbouring beats—and had employed the word “*tetanus*.” He shows that it may result as a first effect of the ligature, and also as a first effect of the circulation of serum.

employed, the cannula on which the heart was tied served as the one electrode, the other electrode pressed against the outer surface of the ventricle, care being taken that contact persisted throughout faradisation. The excitations were very frequent, the hammer of the induction apparatus vibrating rapidly.

The results obtained were in accordance with the previous statements from Marey, and it became clear that *fusion*, complete or incomplete, *i.e.* tetanus, complete or incomplete, could be produced in the following ways, viz.:

1. By lessening the refractory period. Increase of the strength of the current will effect this. Raising the temperature will do the same. Further, certain drugs will do the same.

Even in the cool months of October and November we met with hearts whose irritability was such that they exhibited this fusion from the onset. It was especially to this form of fusion that Luciani drew attention.

2. By prolonging the duration of each contraction. It is obvious that, other things remaining the same, increase in the duration of the beat must favour fusion. Some drugs, *e.g.* soda, ammonia, and its salts, probably act in part in this way.

3. Yet another way is to be noted. Certain drugs, *e.g.* soda, ammonia, potash, antiarin, digitalin, strophanthus, induce a persistent spasm of the ventricle, not, however, by means of a fusion of beats, for these may occur so infrequently as to exclude this mode; in such cases, even when the intervals between the beats are a minute or more, the persistent spasm may last during the whole period of the intervals. This persistent spasm will, *cæt. par.*, tend to fuse together neighbouring beats.

It has been suggested ('Journal of Physiology,' December,¹ 1881) that this spasm may be an increase of the tonus of the heart and allied to contracture.

¹ "Regarding the action of Hydrate of soda, ammonia and potash on the Frog's Ventricle."—Sydney Ringer, M.D.

The effect of temperature was tested, and it was found that whilst heat facilitated the production of tetanus, cold hindered such; these results are confirmatory of Marey's statements as to the refractory period. A difference of temperature amounting to 12° C. demonstrated the above very distinctly.

As to the effect of exhaustion, this does not appear to affect the facility with which the heart may be tetanised.

It is worth while contrasting cardiac tetanus with that of a skeletal muscle. In the latter case a stimulus sufficient to excite a good contraction will, if sufficiently frequently repeated, yield tetanus. In the former, a stimulus capable of causing full contraction of the heart, but not in excess of such strength, will not yield tetanus by repetition, however great the frequency attained. The explanation is to be found in the refractory phase attending each contraction. To get tetanus the strength of the current must be increased, whereby the refractory period is diminished up to extinction.

Diagram 1, fig. I, represents the development of tetanus. The figures above the line indicate the positions of the secondary coil of the Du Bois Reymond.

In A we have incomplete fusion; the frequency, though increased, is insufficient to effect complete fusion.

In B the effect of increased strength of current is seen to have caused greater frequency and completer fusion.

In C a further stage is shown, but here, with the secondary coil at 3, also with the coil at 5 in D, the individual beats can no longer be counted, the line being in parts practically straight.

In addition to increased frequency, both B and C show that the element, persistent spasm, is also present as a factor. The length of line above the trace represents the time of faradic excitation.

Having described the effect of continuous faradisation on the heart, we proceed to describe how this effect is modified under the influence of certain drugs.

The mode of experimentation was the following :—The

effect of faradisation was tried before the addition of the drug, and a certain degree of tetanus being selected to serve as standard, the addition of the drug was commenced; the secondary coil was maintained, of course, stationary, and at definite, equal intervals of time the heart was faradised. The intervals were eight or ten minutes in length, sufficient to allow the residual effects from the preceding tetanus to have passed off.

Hydrate of soda, hydrate of ammonia, hydrate of potash.

Hydrate of soda increases the readiness with which the heart answers to continuous faradisation. Thus, a strength of current capable only of slightly increasing the frequency of the normal beats, therefore short of producing tetanus, caused well-marked tetanus after the addition of soda. In this tetanus all three factors are probably at work, viz. diminished refractory period, persistent spasm (of the nature of tonus), increased duration of each beat. This increased readiness of response occurred without any diminution of the height of the trace. In the doses here used, then, soda increases what may be termed excitability, without affecting contractility (Diagram 1, fig. II, A, B, C).

From these observations, made in November, season (temperature?) would seem to have a modifying influence. The dose of soda required to produce a given effect here was much larger than in summer, and the diastolic contraction, so well marked in summer, was much less developed, and then only after a relatively large dose.

Hydrate of ammonia.—The excitability to the continuous faradic is considerably increased, whilst the height of the beat is still undiminished. This increased excitability is maintained during the early part of the decline in height, then itself begins to decline, but even to the last the excitability remains, at least, as good as before the addition of ammonia (Fig. III, A, B, C, D).

The modifying action of season was marked here also. In summer a much smaller dose is requisite to develop

well-marked diastolic contraction and the persistent spasm indicated by departure from the base line, which spasm increasing, the ventricle finally stops in strong systole, in which condition it remains a considerable time. In the present series, made during November, the above effects were not strongly marked except a very large dose was administered.

Hydrate of potash.—The readiness to become tetanised is markedly decreased by potash, and a strength of current sufficient to give well-marked tetanus before addition subsequently soon loses its effect. A rather curious effect is further to be noted: not only may such current fail to show any tendency towards producing tetanus, it may actually suppress the spontaneous beats, these beginning again a little time after discontinuance of the faradisation (Diagram 2, fig. IV, A, B, C, D, E, illustrate potash). This suppression of the spontaneous beats is not shown in diagram.

Contrasting the effects of soda, ammonia, and potash, we have, on the one hand, soda and ammonia, which early and for a considerable period increase the excitability of the cardiac tissue, as tested by continuous faradisation; on the other hand, potash, the striking effect of which is a diminution of this excitability from the very commencement. This diminished excitability occurs, even though at the time there exist persistent spasm due to the drug (Fig. IV, c, shows this well).

It may be here stated in general terms that, so far as have been examined, the salts of potash act like the hydrate in the way in which they modify the effect of continuous faradisation, *i. e.* they lessen this from the commencement, and may further cause the suppression of spontaneous beats during faradisation above noted.

In the present series the iodide and citrate were tested on this point; the chloride had been previously examined (see the 'Practitioner' for January, 1882).¹

¹ "Concerning the action of the Chlorides and Bromides of sodium, ammonium, and potassium on the Frog's Ventricle," by Sydney Ringer, M.D.

The fact of the citrate—an organic salt—conforming with the inorganic salts, the iodide and chloride, renders the presumption that salts of potash generally may behave alike in the above respect not improbable.

The other mode of testing the influence of drugs has now to be considered, viz. "*the action on the spontaneous working of the heart.*"

The drugs tested in this direction were of the bases—hydrate of potash alone—of the salts, the iodides, bromides, and chlorides of sodium, ammonium, and potassium, also the citrates of these three bases. Incidentally the modification of the effect of continuous faradisation was examined in the case of the iodides. The results of the experiments will be first detailed, and then the conclusions given to which these led.

The mode of experimentation has already been stated. The strength of the solutions employed was in each case 10 per cent. The quantities of this used are given in cubic centimètres, and the actual quantity of salt in grammes and grains. The quantity of blood mixture used was throughout 100 cubic centimètres.

The reason why of the bases, potassium hydrate alone was taken was that the tendency which the other bases—soda and ammonia—show to produce arrest of the heart in full systole, does not allow of a quantitative comparison between the drugs, since potash arrests in diastole.

Caustic potash.—The salient feature here noted was the persistent spasm excited, but, disregarding this, the effect on frequency, so far as the primary effect went, was inconstant, sometimes slowing, sometimes quickening, but in all cases marked slowing preceded complete inhibition, which occurred in all six cases, and on an average after 0.6 c.c. (= 0.9 grains) had been added and whilst the ordinate was of good value.

When in the final stage single stimuli caused no response, continuous faradisation was without effect.

With regard to the height of the beat, this was not much affected in the early stage, but chiefly towards the

end, and in particular after complete inhibition. No primary increase in height was noted such as ammonia shows. The persistent spasm or diastolic contraction, which has been previously described ('Journal of Physiology,' Dec., 1881), was here particularly well marked.

The quantities required to arrest the heart were :

Exp. I.—Feb. 7.	Temp. of room	15° C.	Quantity	0.75 c.c.
„ II.— „ 7.	„	15.5°.	„	0.85
„ III.— „ 8.	„	15°.	„	1.05
„ IV.— „ 9.	„	14.5°.	„	1.05
„ V.— „ 9.	„	15°.	„	0.95
„ VI.— „ 10.	„	15°.	„	0.65
				5.3

∴ Average 0.88 c.c. = 0.088 grms. = 1.35 grains.

Iodide of sodium.—The effect on the rhythm observed here was a slight lessening of the frequency of the beats, but in no case were these arrested, so that the beats remained spontaneous to the very end, *i.e.* as long as contractility persisted. The heart is arrested in diastole.

In the final stage, when the beats had quite disappeared or showed only as a faint waviness of the trace, and single induction shocks would either give no response or one only just visible, continued faradisation of the same strength or weaker would cause persistent spasm, reaching a maximum by successive steps, each contraction being piled up, as it were, on the top of the preceding one. (See Diagram 3, fig. VII A.

In connection with this it must be mentioned that occasionally, whilst the heart was beating spontaneously but under the influence of the sodium salt, a somewhat similar piling up was observed, occurring without obvious cause.

This phenomenon has been referred to throughout this paper, and the expression "*piling up*" retained, but it must be stated that this mounting up by a succession of steps is not always seen; the term has, however, been kept, and for this reason it must be remembered that the essential part of the phenomenon is the height attained,

which is far in excess of any individual contraction spontaneous or excited. (See fig. VII, A and B.)

As to the effect on contractility the amplitude of the beat gradually lessens, but in the end stages, when the height has been greatly reduced, the breadth of the trace, *i.e.* the duration of the beat, becomes increased, in some cases very considerably.

Iodide of sodium is very little poisonous, as will be seen from the quantities appended, which were those requisite to stop the heart:

Exp. I.—42 c.c.	Temp. at time of experiment	12·5° C.
„ II.—72	„	10·5°
„ III.—48	„	10°
„ IV.—54	„	9·5°
„ V.—52	„	9°
„ VI.—60	„	8·5°
328		

Average 54·6 c.c.=5·46 grms.=84·24 grains.

Iodide of sodium lessens in a marked degree the excitability to continuous faradisation.

Iodide of ammonia.—This is an unstable salt, readily yielding free ammonia and iodine. A good commercial specimen was used, containing, however, traces of the above.

The effect on rhythm is not marked, spontaneous beats continuing till contractility is nearly, if not quite, destroyed; in this respect ammonium iodide agrees with the corresponding sodium salt. The heart is arrested in diastole.

After the heart has been arrested, neither single induction shocks, nor continuous faradisation, has any effect. In this respect the salt contrasts with sodium iodide.

The heart is arrested by the destruction of contractility, the beats growing weaker and weaker till they finally disappear. There is, however, probably in all cases an early stage during which the ventricle empties itself more completely, *i. e.* a stage of stimulation; this is scarcely appreciable when the ventricle is contracting vigorously before

addition of the drug, but when failing to empty itself quite, the above stage is indicated by increased amplitude of the trace, and with this increased height rounding of the top of the trace is noted. If a large dose be suddenly added, both diastolic contraction and persistent spasm appear. In one case, as the effect of a large dose, spontaneous beats were arrested and replaced by a slowly remitting spasm.

This salt is a far more powerful paralyser of the ventricle than iodide of sodium. Six experiments gave the following numbers :

Exp. I.—4·6 c.c.	Temp. at time of experiment	12° C.
„ II.—4·9	„	12°
„ III.—4·2	„	13°
„ IV.—3·9	„	13·5°
„ V.—4·9	„	13·5°
„ VI.—2·1	„	14°
24·6		

Average 4·1 c.c. = 0·41 grms. = 6·3 grains.

Iodide of ammonium, like iodide of sodium, lessens in a marked degree the effect of the continuous faradic current. Suppression of the spontaneous beats during faradisation may even be witnessed (see Potash).

Iodide of potassium.—The striking feature in the action of this salt is that suddenly, whilst the height of the trace is still considerable, the spontaneous beats are arrested permanently, though there is still response to electric stimulation. If the addition of the drug be still continued the response, originally having the value of the last spontaneous beats, grows less and less till finally contractility disappears. Preceding the arrest of spontaneous beats these latter grow more infrequent. During lengthened intervals between spontaneous beats, or subsequently to permanent arrest, the less the interval since the last spontaneous or excited beat the stronger must be the excitation to be effectual. This of course between limits, for below a certain strength all excitations would be ineffectual, above a certain strength all would be effectual. The

same applies to a heart temporarily inhibited by the ligature. In fact, the ventricle arrested by iodide of potassium behaves in all respects like such heart.

When the contractility has disappeared to single induction shocks, continuous faradisation is without effect; in this respect it resembles iodide of ammonium, but contrasts with iodide of sodium.

Iodide of potassium further acts powerfully on contractility; this is seen, subsequent to arrest of the spontaneous beats, in the decreasing height of the excited contractions.

The following numbers were obtained:

Exp. I.—2 c.c.	Temp. 13° C.
„ II.—2	„ 15°
„ III.—2·2	„ 13°
„ IV.—2·2	„ 14·5°
„ V.—2	„ 15°
„ VI.—1·9	„ 9·5

12·3

Average 2·05 c.c. = 0·205 grms. = 3·16 grains.

In its lessening the effect of continuous faradisation of the ventricle, iodide of potassium is similar to iodide of ammonium, but more powerful; as with this latter, in the final stages before complete arrest, the spontaneous beats become arrested during the faradisation, and a considerable interval may follow before the spontaneous beats recommence. In this latter respect it, with the ammonium salt, contrasts with sodium iodide.

A character shown in common by the iodides of all three bases was that, subsequently to the arrest of the ventricle by the drug, and when single electric shocks were without effect (also continuous faradisation in the case of ammonium and potassium iodides), the dilution of the circulating fluid with water (100 c.c. were in each case added) brought back spontaneous beats of good value; the recovery was but temporary, but in some cases a second and a third dilution (100 c.c.) were attended with

recovery, each time feebler and of shorter duration. With each recovery a certain amount of persistent spasm occurred, indicated by the trace retreating from the base line.

Bromide of sodium.—Six experiments were made. The effects were somewhat inconstant and anomalous; thus in two cases there was no inhibition whatever, the beats remaining spontaneous till contractility disappeared. These, then, were in accordance with the iodide and citrate of soda series. In one there was distinct inhibition, as marked as in the case of potassium salts. In the remaining three the rhythm was curiously affected, *e.g.* after the quantities had reached 15 c.c., 15 c.c., and 18 c.c. respectively, patches of beats separated by long intervals occurred, the end patch was of long duration, the beats frequent, and the rhythm persisting till contractility had disappeared. Though this phasic condition represents a form of inhibition, still it was not complete inhibition, and in five out of the six the final stages contrasted as markedly with the effects of potassium salts as did those of the other sodium salts.

In the final stage, when the strongest current excited either no response or only the faintest, the characteristic piling up was obtained with continuous faradisation. There was nothing special as to contractility. In the one instance of marked inhibition there was scarcely any reduction in height when this occurred.

The quantities were :

Jan. 19	.	.	.	Temp. 14.5°	...	42 c.c.
„ 24	.	.	.	„ 18°	...	32
„ 24	.	.	.	„ 17.5°	...	41
„ 26	.	.	.	„ 17°	...	34
„ 27	.	.	.	„ 17°	...	28
„ 27	.	.	.	„ 17°	...	24
						201

Average $33.5 = 3.35$ grms. = 51.7 grains.

Bromide of ammonium.—The results obtained were very

uniform. In all, frequency was increased ; in five, this occurred from the very beginning of addition of the drug, in one, rather marked slowing followed the first dose, but soon gave way to increased frequency. The increased frequency was maintained up to the end, disregarding some slight irregularity which in three cases appeared in the final stage.

Subsequent to the disappearance of spontaneous beats, there was no response to single shocks, and none to continuous faradisation.

On contractility, a primary effect in the way of increase of the height of the beat with broadening of the apex was distinct in some, very slight in others, but discoverable in all. Slight departure from the base line was also noticed, but not in all. The frequency of beats was too great to admit of diastolic contraction appearing. These last-named effects were early, viz. after the first or second dose. Fig. V A (Diagram 2) illustrates these effects.

The decline in height was rather rapid towards the end.

Quantities :

Jan. 28	.	.	Temp. 16·5°	...	Quantity 2·6 c.c.
„ 28	.	.	„ 16°	...	„ 2·4
„ 30	.	.	„ 16°	...	„ 2·2
„ 30	.	.	„ 16·5°	...	„ 2·4
„ 31	.	.	„ 16°	...	„ 2·6
„ 31	.	.	„ 17°	...	„ 2·2
					14·4

Average 2·4 c.c = 0·24 grms. = 3·70 grains.

Bromide of potassium.—In the six experiments made with this drug the effect in the way of inhibition was less marked than was the case with the other salts of potassium examined, viz. iodide and chloride. In general, moreover, there was less uniformity of action in the series.

In three out of the six complete inhibition obtained ; in the remaining three, though in the final stages, the inhibition was almost complete, still, an occasional spontaneous beat occurred till the amplitude was practically abolished.

The effect, then, though somewhat less marked here, is still very decided.

In five out of the six cases slowing occurred as a primary effect, contractility suffering but slightly; the subsequent effects on rhythm were very irregular.

As to the effect of continuous faradisation, no piling up of the beats obtained as a final effect.

There is nothing special as to the effect on contractility excepting that the action hereon was not marked early. At the time of complete inhibition the beats were severally reduced to $\frac{3}{5}$, $\frac{1}{2}$, and rather less than $\frac{1}{2}$ their original height.

Quantities employed :

Jan. 19	.	.	1·7	...	Temp. 15°
„ 20	.	.	2·1	...	„ 17°
„ 20	.	.	2·4	...	„ 18°
„ 21	.	.	2·8	...	„ 14·5°
„ 21	.	.	2·2	...	„ 15°
„ 23	.	.	1·6	...	„ 13·5°
12·8					

Average 2·13 c.c. = 0·213 grms. = 3·28 grains.

Of the bromide series the effect of dilution was tested with the ammonium and potassium salts. Dilution with blood mixture was substituted for dilution with water, 100 c.c. being added. Dilution was tried twice with ammonium bromide with negative result; no recovery occurred. With potassium bromide dilution in three cases brought back spontaneous beats of good height. The blood mixture was added when the ventricle had ceased to respond to the strongest stimulation.

Chlorides of sodium, ammonium, potassium.

Some experiments on these salts made in the summer months have already been recorded.¹ But as season

¹ 'Practitioner,' January, 1882.

(temperature ?) affects the action of remedies on the frog's heart the experiments were now repeated in January, that we might be able to compare the action of the chlorides with that of the iodides and bromides at the same time of the year.

Chloride of sodium.—As in the case of bromide of sodium, the effect on frequency was somewhat inconstant.

In one case, with the exception of trifling slowing, there was no effect on frequency, the beats remaining spontaneous to the end.

In two there occurred distinct inhibition quite of the potash type.

In a fourth marked slowing was produced, amounting in the end stages to inhibition, almost complete.

Lastly, in two cases the action of the ventricle became phasic, groups of beats alternating with intervals, this condition remaining to the end.

Here, though there was distinct disturbance of rhythm, spontaneous beats still persisted to the end. So that we have three cases of non-inhibition against three cases of inhibition.

Continuous faradisation, after arrest of the ventricle, gave the characteristic piling up.

The quantities required to arrest the heart were :

I.—Feb. 1.	Temp. of room	16°.	Quantity	16 c.c.
II.— „ 1.	„	16·5°	„	14
III.— „ 2.	„	—	„	20
IV.— „ 4.	„	17°	„	23
V.— „ 4.	„	17°	„	18
VI.— „ 6.	„	9·5°	„	25
				116

Average 19·3 c.c. = 1·93 grms. = 29·77 grains.

Chloride of ammonium.—The effect on frequency was a slight increase of the contraction rate ; the beats were accelerated on an average in the proportion of from three to five, three being the original frequency

In one case the beats became slightly slower throughout

but in this, as in all the others, spontaneous beats of good frequency persisted to the very last, *i.e.* till contractility disappeared.

When the heart had been arrested and single induction shocks caused no response, continuous faradisation was equally without effect.

This salt acts powerfully on contractility, the beats growing less and less till final cessation in diastole.

In all six experiments, as a first effect and for a short time the beats increased in height and became broader; in three this was very distinct, in the other three it was but slight; in the former there was also departure from the base line, showing a certain amount of persistent spasm.

The quantities required to arrest the heart were :

I.—Jan. 16.	Temp. of room	17° C.	Quantity	2.1 c.c.
II.— „ 16.	„	18.5°	„	2.1
III.— „ 17.	„	17°	„	2.
IV.— „ 17.	„	16°	„	1.8
V.— „ 18.	„	18°	„	1.8
VI.— „ 18.	„	18°	„	1.8
				11.6

Average 1.9 c.c. = 0.19 grms. = 2.93 grains.

Chloride of potassium.—The first or second dose always caused slowing, then, in five out of the six cases, the beats again became more frequent, in some instances beyond the original frequency; then the beats again became slower with intervals, now amounting sometimes to from three to four minutes. This occurred on an average after 0.5 c.c. had been added. After as much as 0.76 c.c. = 1.17 grains, on an average, had been added, spontaneous beats ceased, though contractions could still be excited by induction shocks. This complete inhibition occurred when the beats were reduced respectively to $\frac{1}{3}$, $\frac{2}{5}$, $\frac{1}{5}$, $\frac{2}{5}$, $\frac{3}{4}$, $\frac{1}{6}$ of their original height.

When single shocks gave no result, continuous faradisation was equally without effect.

Contractility was completely destroyed after the addition of the following doses :

I.—Jan. 12.	Temp. of room	17° C.	Quantity	1·4 c.c.
II.— „ 12.	„	17°	„	1·5
III.— „ 13.	„	15·5°	„	1·8
IV.— „ 13.	„	16·5°	„	1·7
V.— „ 14.	„	19·5°	„	1·8
VI.— „ 14.	„	18·5°	„	1·6
				9·8

Average 1·6 c.c. = 0·16 grms. = 2·46 grains.

In respect of the discussion of the results obtained, it may be mentioned that this discussion has assumed the cardiac muscular tissue to possess the property of rhythmic contractility apart from ganglionic structures.

Since the paper was written Dr. Gaskell's paper, read before the Royal Society, has reopened this question. The results here obtained, however, as also the discussion of these, are in nowise affected by this question as to rhythmic contractility necessitating two structures, nervous and muscular, or but one structure, viz. muscular. That which is alone required here is a rhythmically contractile tissue ; this given, we here show that the action of drugs on such demonstrates the dissociation of that which underlies "*contraction rate*" or "*rhythm*," from that which underlies "*contraction height*."

The actual results obtained have been so far alone given ; of these, certainly the most striking is this—that given a rhythmically contracting tissue, the action of a drug on this may show itself in two directions :

1st. As affecting the intervals separating successive beats.

2nd. As affecting the actual value of the beats themselves.

Thus we have seen drugs affecting the frequency or contraction rate, and also the height of the individual beats (this last has been always referred to as the action on contractility). The stress has fallen now in one direc-

artificial saline solution was circulated through the heart tied on to the perfusion cannula of a Roy apparatus by a ligature placed in the auriculo-ventricular groove. To this solution was then added the particular drug under experiment. The results were as follows:—Digitaline, strophanthus, dyak, scillitine, convallamarin, all caused persistent spasm of the ventricle, in varying degree however, digitaline being by far the most active in this respect. The experiments on barium chloride have already been given elsewhere ('Brit. Med. Journ.' Aug. 11th, 1883); they too showed persistent spasm as the result of direct action of the drug on the heart. Similarly experiments made in 1882 with the hydrates and carbonates of potassium and sodium,¹ showed persistent spasm to result from direct action on the excised ventricle, with the notable exception, however, of sodium bicarbonate which is there recorded as not producing persistent spasm. This exception then would accord with the results obtained for the vessels.

In the last-mentioned experiments it was noted that the bicarbonate of potassium caused much less persistent spasm of the ventricle than did either the carbonate or hydrate. These experiments were repeated now with like results. It was, however, observed in addition that the adding of sodium bicarbonate to a saline solution not containing a potassium salt (in physiological dose) did cause persistent spasm. This at first led us astray, showing as it appeared to do a difference in the action of the sodium bicarbonate on heart and vessels. When, however, we made the experiments exactly comparable by adding a physiological quantity of a potassium salt to the pure saline, or instead of this employed saline made with tap water in place of distilled water (the former containing the necessary trace of potassium salt), when this was done the discrepancy disappeared, and the heart behaved just as the vessels had done. It must be remembered that the saline fluid employed to circulate through the vessels was made with tap water.

¹ *Vide* 'Practitioner,' Aug., 1883, "On the individuality of action of the component parts of a drug."

We did not mention aconitia among the foregoing experiments on the tortoise; this drug, however, was tried with the result of apparently causing dilatation of the vessels. When, however, tested on the excised frog's heart an opposite result obtained, viz., spasm of the heart muscle. We suggest that the following may possibly explain this seeming contradiction; the heart possesses the property of rhythmic contractility, and we have elsewhere shown that, where there is a tendency to persistent spasm of the ventricle, the rhythmic contractions accentuate their spasm or appear to develop it. In the present experiments on the heart with aconitia the spasm was in connection with rhythmic contractions, and when these were prevented as by ligaturing the ventricle through its upper third, the spasm did not develop. Should this explanation be the true one, this second discrepancy would be apparent only.

Thus far we have seen the direct action on the vessels to be similar to that on the heart; there yet remains for determination the question as to whether any of the effect on the vessels is to be attributed to nervous agency, *i.e.*, whether in addition to direct action on the vessels, these may be influenced reflexly through the nervous system. The following experiment was designed to answer this:—The cerebral and optic lobes were destroyed, care being taken to ensure there being the entire thickness of the cerebellum between the surface of section and the fourth ventricle. We may thus take it that the vaso-motor centre was uninjured. From the brainless tortoise the whole abdominal shell wall was then removed, and the peritoneum carefully separated up from the shell wall; it was then opened longitudinally, the descending aorta exposed, ligatured proximally and a cannula tied in distally. The large vein running up in front of the lung to the liver was then exposed and ligatured proximally; the same was done for the two large veins in the anterior abdominal wall. All three veins were then opened distally, and the saline solution started as for the previous experiments.

By the means adopted a free outlet from the veins was provided for the inflowing saline, and the escaping fluid could be caught and measured as in the foregoing experiments. In addition to this the vessels through which the saline was flowing were under central nervous control, since the spinal cord, including the medulla with its vaso-motor centre, was intact. The poison was then injected into the muscles of the back of the neck.

Two experiments were made with digitaline ; of these the first gave purely negative results, just as occurred in two out of the three experiments made after the same method with barium chloride. The digitaline when injected into the muscles remained without effect on the saline circulation, and even when added to the saline solution itself it failed to produce any very definite effect. The second experiment gave similarly a negative result for the injection of the poison into the anterior circulation, but on adding the drug to the saline circulation the tissues at once reacted. We record the details of this experiment.

June 27th.—Temperature 18° ; head of pressure 30 centimetres, maintained constant within 0.5 centimetre.

Rate of outflow per five minutes in c.c.—29,¹ 29, 26, 29, 30, 32,² 33, 33, 37, 42, 43, 48,³ 46, 52, 50, 46, 55, 53,⁴ 43, 12, 2.

¹ Simple saline solution (made with tap water), 0.6 per cent. ² Digitaline, 1 per cent. 1 c.c. injected into muscles of neck in 0.5 c.c. doses. The ventricular contractions seemed to increase in vigour, but the diastoles remained good, or even more complete. Rhythm somewhat irregular. ³ Digitaline, 1 c.c. injected in 0.5 c.c. doses, as above. Both diastole and systole remained good. ⁴ Digitaline, 1 c.c. *added to the saline circulation.*

The brain cavity after completion of the experiment was more completely opened and the brain found to have been destroyed at the level of the posterior part of the optic lobes ; cerebellum apparently intact.

Assuming the poison to have been absorbed then it must have been pumped by the heart to the vaso-motor centre, yet it appears to have been unable to influence the calibre of the vessels of the hinder extremities, which

latter the final addition of digitaline to the saline circulation itself proves to have been ready to respond.

The very free vascular anastomosis which obtains in the tortoise may at first sight appear to invalidate the experiment, since it scarcely allows of complete isolation of the two circulations. This objection would certainly hold had we obtained a positive result, *i.e.* had the injection of the poison into the anterior circulation caused contraction of the vessels of the posterior circulation, since the poison might have entered the latter through the anastomoses; it can, however, scarcely stand for a negative result.

Finally, there remains for us to record some experiments made on warm-blooded animals with digitaline.¹ This drug alone was selected as typical of the group, and the warm-blooded animals were experimented on in order to complete the series and bring our results a step nearer to human physiology.

The apparatus we employed was very similar to that used by Glax and Klemensiewicz in their experiments on artificial circulation.² A large air-chamber in connection with a force-pump allowed us to get up pressure. The efferent tube from the air chamber was put in connection with two three-necked Woolf bottles by a T tube, both arms of the T tube being provided with clamps. Into each of the Woolf bottles a mercury manometer was inserted, and, finally, from the third neck of each bottle an efferent tube was brought into connection by means of a T tube with the cannula for the aorta. Each afferent tube was provided with a clamp. Each Woolf bottle was of large capacity and was filled with the saline fluid for circulation. Both stood in a large water-bath, which was maintained at a constant temperature of 39° to 40° C. The use of the two bottles was to allow of the filling of the spent bottle without stopping the flow or altering the pressure. And

¹ We are indebted to Professor Schäfer for having kindly performed these experiments for us.

² 'Beiträge zur Lehre von der Entzündung. Sitzungsberichte der Wiener Akademie,' Bd. lxxxiv, Abth. iii, p. 216.

this was readily managed by simply clamping off the tube leading from the pressure bottle to the spent Woolf bottle and opening the tube leading to the other, and similarly opening the efferent tube from the latter and closing that from the spent bottle. By keeping a large stock supply of the artificial circulating fluid also immersed in the bath we were able to replenish the bottles whilst maintaining the temperature of this fluid nearly constant. We will first of all give an experiment in which the fluid was not poisoned, the saline circulation being maintained right through. This gave us our control experiment and showed us the limits of variation independent of drug action.

July 13th.—Temperature of room 23° C.; experiment on a cat.

Temperature of bath 39° — 40° C.; artificial circulating fluid = simple tap water saline 0·6 per cent. + a physiological trace of potassium chloride, viz. 0·7 c.c. of a one per-cent. solution to the 100 c.c. saline. Pressure 100 mm. Hg. The animal was chloroformed, the abdomen opened by an incision in the linea alba, the inferior cava and descending aorta exposed and both vessels ligatured proximally. Into the descending aorta the afferent cannula was then inserted distally and tied in; into the inferior cava the efferent cannula was likewise inserted distally and tied in. The experiment was then started.

During the whole experiment up to the death of the animal narcosis was maintained so that the experiment was painless.

Rate of outflow per five minutes in c.c.—300, 240, 310, 380,¹ 415, 380, 335, 320,² 265, 155, 170,³ 170, 190, 180, 200,⁴ 175, 175, 150,⁵ 130, 130, 120,⁶ 115, 100, 85,⁷ 75, 65,⁸ 100,⁹ 120, 110.

¹ No œdema so far. ² Animal dying. Doubtfully slight œdema of tissues. ³ Animal dead. Distinct œdema. ⁴ Œdema marked. ⁵ Leakage from the tissues exposed in the wound, especially from the surface of the intestines. The leakage is due to simple sweating through the tissues. ⁶ Skin of legs quite tense from the œdema. ⁷ Skin very tense. ⁸ Free incision through skin and subcutaneous tissue of one leg. ⁹ Free incision into other leg.

The experiment teaches several things; in the first place the rather considerable variations in the rate of flow in the early stages before the change was in any particular direction. Then with oncoming œdema the steady and somewhat rapid fall in the rate of flow till from a rate of flow of from 300 c.c. to 400 c.c. per five minutes it has fallen to 65 c.c. in the five minutes. That this effect was largely the result of the œdema, we learn not only from the advance of the two *pari passu*, but also from the effect of the free incisions, which lessening tension at once allowed a freer circulation.

The figures representing the rates of flow subsequent to the incisions are certainly lower than they should be, and probably decidedly lower since from the large surface of the incision considerable oozing took place which in part would represent escape through some of the smaller cut vessels, and by this quantity the above numbers would be deficient.

To contrast with this we give the following experiment.

July 9th.—Temperature of room 20° C.; experiment on rabbit.

The same apparatus was employed, but the stock supply of saline was not so large as in the previous experiment, and the through flow was so rapid that, though the bath was maintained at a constant temperature of about 40° C., the saline supply must have been below this temperature, therefore the temperature conditions were less satisfactory. The saline was of the same composition as in the previous experiment, the pressure in the manometer was 50 mm. Hg.

The animal was kept under chloroform throughout the experiment.

Rate of outflow per five minutes in c.c.—178, 188, 174, 270, 310,¹ 102, 80, 16, 14,² 8, 8, 9, 10, 11, 13,³ 13, 14, 14, 16, 16, 16, 19, 20, 16, 19,⁴ 17,⁵ 17, 14.

¹ Digitaline 1 per cent., 1 c.c. to 100 c.c. saline. ² Unpoisoned saline re-substituted. ³ Animal dead. ⁴ Marked œdema. ⁵ Incision into subcutaneous tissue to try and free the vessels.

Making all allowance in this experiment for the temperature not being quite constant, the results are yet too striking to admit of any other interpretation than that the digitaline did act directly and powerfully on the vessels. If the numbers be compared with those in the previous experiment this will be at once apparent. It will be observed that the resubstitution of saline did not appreciably improve the circulation; with reference to this, however, it must be remembered that the rate of flow at the time of resubstitution was exceedingly slow, and hence it would naturally take a long time to wash through the vessels; further, that in the later stages the increasing œdema was an obstacle to improvement, and finally, that the tissues of warm-blooded animals are much more delicate, and hence less likely to recover from damage done. That the incision into the tissues should be without effect will be comprehensible on similar grounds.

Another experiment on a cat was made in which, after establishing a saline flow, digitaline was injected into the subcutaneous tissue, of the anterior or heart circulation. The results obtained were negative, but the apparatus employed was rather less convenient than the above described, and various sources of fallacy crept in.

Confining our attention, however, to the two experiments just described, we find the results in keeping with those already obtained with cold-blooded animals, and we think the present series of experiments establishes tolerably definitely the direct action of digitalis and the group of bodies of which it is the type on the vessels.

To complete the argument which we stated at the commencement of the paper, experiments were made to ascertain the degree of poisonous action of these drugs on the skeletal muscles. Definite quantities of the drugs were injected beneath the skin of the back in frogs, and subsequently to systemic death, or in some cases even before, the muscles tested electrically as to their excitability.

The following were the results obtained :

Digitaline. 1 per cent. solution.

Weight of frog.	Quantity injected.	Condition of muscular irritability.
34 gms. ...	0.3 c.c.	... Systemic death in 3½ h.; muscular irritability gone in 6 h.
18.5 „ ...	0.2 c.c.	... Muscular irritability gone in 5 h. 30 m.
31.5 „ ...	0.2 c.c.	... Frog quite well after 19 h.
16.5 „ ...	0.2 c.c.	... Muscular irritability gone in 4 h. 45 m.
11 „ ...	0.2 c.c.	... Muscular irritability gone in 3 h. 25 m.
? „ ...	0.4 c.c.	... Systemic death in 1 h. 20 m.; muscular irritability fair after 3 h. 25 m.

Strophanthus. The crude drug.

25.5 gms. ...	0.2 c.c. (2.5 %)	... Lost in 2 h. 20 m.
{ 25.75 „ ...	0.2 c.c. (1 %)	... Lost in 2 h. 40 m.
{ 14.75 „ ...	0.2 c.c.	... Lost in 2 h. 30 m.
{ 10.75 „ ...	0.2 c.c.	... Lost in 2 h. 40 m.
{ 32 „ ...	0.2 c.c. (5 %)	... Lost in 1 h. 10 m.
{ 12 „ ...	0.2 c.c.	... Nearly gone in 1 h. 30 m.
{ 10.5 „ ...	0.2 c.c.	... Nearly gone in 1 h. 30 m.
{ ? „ ...	0.4 c.c.	... Quite gone in 2 h. 45 m.

Dyak. The crude drug; but one experiment.

22 gms. ...	0.2 c.c. (1 %)	... Lost in 1 h. 20 m. (Systemic death in 50 m.)
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Scillitine.

31 gms. ...	0.2 c.c. (1 %)	... No effect; frog normal.
38 „ ...	0.3 c.c. „	... No effect; frog normal.
45 „ ...	0.5 c.c. „	... Muscular irritability lost in 6 h. Systemic death in 2 h.
18.5 „ ...	0.2 c.c. „	... Muscular irritability nearly gone after 20 h.

Barium chloride.

23 gms. ...	0.5 c.c. (10 % solution)	... Lost in 3 h. 15 m.
19.75 „ ...	0.3 c.c. „	... Lost in 3 h. 15 m.
20.75 „ ...	0.2 c.c. „	... Lost in 3 h. 15 m.
20.75 „ ...	0.3 c.c. „	... Still slight persistence after 3 hours 15 minutes.

ACTION OF THE DIGITALIS GROUP.

Weight of frog.	Quantity injected.	Condition of muscular irritability.
23.75 „ ... 1 c.c. (1 % solution)		The frogs developed within the first few hours peculiar stiff movements and the cry-reflex described by Boehm; from this state they for the most part recovered, and at the end of 24 hours were fairly normal.
24.75 „ ... 0.5 c.c. „		
27.5 „ ... 0.5 c.c. „		
? ... 0.2 c.c. „		... No effect.

Examining these results we observe in the first place that the above drugs from the digitalis group are all *notable poisons to the skeletal muscles*. And we observe, further, that strophanthus and dyak poisons act most powerfully in this respect. It is true that some of the experiments with strophanthus were with 2.5 per cent. and 5 per cent. solutions as against 1 per cent. of digitaline, but then we must bear in mind that of the former we were employing the crude drug as against the active principle itself in the latter case. Hence it is clear that both of these drugs, strophanthus and dyak, affect more powerfully the voluntary muscles than does digitaline. If, now, we refer back to their action on the heart we shall find that whereas the chief feature in the digitaline action is the contracture excited, which may be almost complete with scarcely any weakening of the heart's action, in the case both of strophanthus and dyak we find that though contracture is well-marked it is less so than with digitaline, whilst at the same time there is more decided weakening of the individual beats. For scillitine the results are less decided; in its action on the skeletal muscles, it scarcely exceeded digitaline in power, whilst on the heart it caused less marked contracture, but decided weakening of the individual beats.

With these results in view we are able to speak less positively as to the possibility of inferring from the action of these cardiac drugs on the heart contractions to action on the skeletal muscles themselves. To determine this point a more extended range of experiments will be needful.

We may now briefly re-state the steps of the argument and sum up the results obtained.

1. Starting from the systolic digitalis heart, which is admittedly a result of direct action on the cardiac muscle, we have found :

2. That for the other members of the digitalis group here examined a like direct action obtains.

3. We have suggested that this local action on the heart, which may affect either the whole heart or a limited portion, according as the drug comes in contact with the whole heart or a limited portion of the heart, that this action may serve as the definition of *digitalis action*, and that such definition would necessarily enlarge Schmiedeberg's already large group.

4. Taking this as the definition we have argued therefrom to local action on the vessels, and have found experimentally such to hold—the digitalis group causing persistent spasm of the arterioles.

5. We have endeavoured to ascertain if the calibre of the vessels may be influenced by these drugs *indirectly* through the nervous system, and, so far as our experiments go, have been answered in the negative.

6. Finally, we have found by experiment that the drugs digitaline, strophanthus, dyak, scillitine, and barium chloride, are markedly poisonous to the skeletal muscles.

The results require some criticism. In the first place, we note that the definition adopted admits into the group such bodies as the caustic alkalies, barium salts, &c. The former certainly do not rank with us clinically as digitalis-like drugs. But it is obvious that clinical use is practical use. And that it must very extensively weed this large scientific group, for it is at once clear that it is practically impossible for us to give alkalies to the extent of alkalinising the system to the degree requisite to bring out the digitalis-like action. Hence the alkalies would be excluded from the clinical group. It is very possible that for similar reasons the barium salt may prove impracticable, and that the gastro-intestinal irritation (vomiting

and purging) excited by the drug, may not allow of its being given in dose sufficient to bring out the cardiac and vascular effects. This point, however, will have to be determined by experience. The like may obtain for many other drugs yet to be included in the digitalis group as above defined, for clinical value is a question of fitness, and results from the fact that the body is an assemblage of organs, and that the action of a drug in many cases is simultaneously on several of these; hence whilst its action on one organ would qualify it for clinical use, by its action on another organ it disqualifies itself.

One other point we would wish to touch upon, viz. the question of the rise of pressure and its dependence on cardiac action. According to Schmiedeberg the blood-pressure rise is due solely to increased cardiac action. "It has been shown," says Schmiedeberg, "to be not attended by diminution in the calibre of the vessels."¹ In view of our own experiments and also of those by Donaldson and Stevens, the results of which have been recently published² (subsequently, however, to the completion of our own experiments both on barium chloride and on the digitalis group), we can hardly accept this statement and hold that part at any rate of the pressure rise must be attributed to narrowing of the calibre of the arterioles. This interpretation indeed appears to us much more in consonance with the data which Schmiedeberg himself furnishes us with, for in the above paper he gives rise of blood-pressure as continuing through the first stage in which there is as a rule slowed pulse-rate, through the second stage in which there is increased pulse frequency, and through the third stage in which there is great irregularity in the heart's action; in the fourth stage, however, with systolic arrest there is rapid fall in blood-pressure. Here we see increased blood-pressure obtaining with most varied heart action, and we can scarcely imagine that in the third stage the cardiac action can be effective in main-

¹ Op. cit.

² 'Journal of Physiology,' vol. iv, pp. 165, *et seq.*

taining the increased tension. Arguing from this we should rather be tempted to exclude the heart and refer all to the vessels; a conclusion, however, which we think would necessarily be faulty, for is not the question one of action and reaction—the heart acts on the arterioles which again react on the heart? It is quite clear that without a peripheral resistance you could never whip up blood-pressure just as clearly as that with no matter how great a peripheral resistance (provided there were still means of out-flow, *i.e.* that the obstruction were not complete) raised blood-pressure could never be maintained with a failing heart. Donaldson and Stevens more especially deal with the question of the work of the heart, though they also take up the question of the condition of the blood-vessels; these latter results being similar to our own. As to the work of the heart they find it diminished. We would, however, suggest that it is possible this resulted from their having pushed the drug too far, for in their experiments on the terrapin, where they record lowered work and also the condition of the heart, we note of this latter that it is very markedly affected; thus, the ventricle is either distinctly shrunken, or there is marked irregularity in its action, or dicrotism, or many auricular beats to one ventricular. In this stage we should scarcely look for increased work of the heart, but should feel rather that we were bordering on stage 4 of Schmiedeberg with fall in blood-pressure.

Papers and References in "The Lancet."

YEAR	VOL.	PAGE	
1862	I	173	On the Temperature, Urea, Chloride of Sodium, and Urinary Water in Scarlet Fever ; and On a Cycle in Disease and Health.
1864	II	675	Testimonial to Dr. Sydney Ringer, of University College Hospital.
1865	II	429	Review. "The Temperature of the Body as a means of Diagnosis in Phthisis and Tuberculosis."
1865	II	512	University College Hospital : The Thermometer in Acute Disease : Case of Renal Inflammation following Scarlatina ; Clinical Remarks.
1865	II	648	University College Hospital : The Thermometer in Specific Fever : Case of Typhoid Fever ; Remarks.
1866	II	208	The Influence of Alcohol on the Temperature of Non-Febrile and Febrile Persons.
1866	II	381	University College : Dr. Sydney Ringer's Address.
1869	I	42	Paper No. 1 on The Therapeutic Action of Drugs : Aconite and its Preparations.
1869	I	392	Paper No 2, ditto : Bromide of Potassium ; Bromide of Sodium ; Bromide of Ammonium.
1869	II	10	Review. Dr. Ringer's Handbook of Therapeutics.
1871	II	752	Ditto.
1873	I	53	Ditto.
1873	I	877	Review. "The Temperature of the Body as a means of Diagnosis and Prognosis in Phthisis."
1873	II	469	Letter by Dr. Ringer on the Accidental Poisoning of Dr. Sharpey ; Recovery.
1874	I	264	On Sulphide of Potassium, Sulphide of Sodium, and Sulphide of Calcium.

YEAR	VOL.	PAGE	
1874	II	338	Ipecacuanha Spray in Winter Cough and Bronchitic Asthma.
1874	II	805	Review. A Handbook of Therapeutics.
1875	I	157	On Jaborandi. By Dr. Ringer and Dr. Alfred P. Gould.
1875	II	907	On Gelseminum Sempervirens. By Dr. Ringer and Wm. Murrell, L.R.C.P., M.R.C.S.
1876	I	82	Ditto.
1876	I	124	Ditto. The Influence of Gelseminum on the Frog's Heart.
1876	I	415	Ditto. The Influence of Gelseminum on Respiration.
1876	I	561	Ditto. Ditto.
1876	I	661	Ditto. Action on Man.
1876	I	732	Ditto. Influence on the Eyes.
1876	I	921	Royal Medical and Chirurgical Society : An Abstract of the following Paper by Dr. Ringer was read : "Observations on Box (Buxus Sempervirens), with special reference to the true nature of Tetanus."
1876	II	78	On Gelseminum Sempervirens. Action on the Pupils.
1876	II	569	Ditto. Action on the Circulation.
1877	I	228	A Suggestion concerning the Condition of the Nervous Centres in Migraine, Epilepsy, and other Explosive Neuroses.
1877	I	499	Review. A Handbook of Therapeutics.
1877	II	198	The Action of Muscarin on the Human Body. By Dr. Ringer and E. A. Morshead, M.R.C.S., L.R.C.P.
1877	II	912	On the Use of Physostigma in some Nervous Affections. By Dr. Ringer and Wm. Murrell, M.R.C.P.
1877	II	950	Ditto.
1878	I	858	On Gelseminum Sempervirens. Gelseminum as a Toxicological Agent.
1878	I	892	On Gelseminum Sempervirens.
1878	II	473	Concerning the Influence of Perspiration on the Febrile Temperature.
1879	I	160	Review. A Handbook of Therapeutics.
1879	I	290	The Action of Pituri on Man.
1880	I	360	On Tonga : A Remedy for Neuralgia, used by the Natives of the Fiji Islands. By Dr. Ringer and Wm. Murrell, M.D., M.R.C.P.

YEAR	VOL.	PAGE	
1880	I	407	Review. A Handbook of Therapeutics.
1880	I	795	On the Mydriatic Properties of Homatropin, with an Account of its General Physiological Action. By John Tweedy, F.R.C.S., and Sidney Ringer, M.D.
1880	II	6	On Glycerine in Flatulence, Acidity, and Pyrosis. By Dr. Ringer and Wm. Murrell, M.D.
1882	I	1033	Royal Medical and Chirurgical Society: Abstract from a Paper by Dr. Ringer and Dr. Harrington Sainsbury concerning the Action of Salts of Potash, Soda, and Ammonia on the Frog's Heart.
1882	II	12	Review. A Handbook of Therapeutics.
1882	II	736	On the Action of the Salts of Sodium, Ammonium, and Potassium. By Dr. Ringer and Dr. Harrington Sainsbury.
1883	I	7	On Manganese in the Treatment of Amenorrhœa. By Dr. Ringer and Dr. Wm. Murrell, M.R.C.P.
1883	I	87	Letter by "Sceptic" criticizing The Paper on Manganese in the Treatment of Amenorrhœa, by Dr. Ringer and Dr. Murrell.
1883	I	628	Concerning the Effects of Dilution and Concentration on the Actions of Poisons.
1883	II	766	Article on Nitrite of Sodium as a Toxic Agent. By Dr. Sydney Ringer and Dr. Wm. Murrell.
1883	II	880	Letter by Dr. Ringer in reply to Dr. Murrell's explanatory Letter on "Nitrite of Sodium as a Toxic Agent."
1883	II	996	Review. A Handbook of Therapeutics.
1884	II	767	Article on the Nervous or Muscular Origin of certain Spastic Conditions of the Voluntary Muscles. By Dr. Sydney Ringer and Dr. Harrington Sainsbury.
1884	II	815	Ditto.
1884	II	860	Ditto. Conclusion.
1885	I	6	Article on an Examination of the Supposed Action exerted by the Antagonism between Acids and Alkalies in modifying the Tonicity of the Heart and Arteries. By Dr. Sydney Ringer and Dr. Dudley Buxton.
1886	I	792	Review. A Handbook of Therapeutics.
1888	II	1082	Annotation. "Ringer's Therapeutics: Strange Advice."

YEAR	VOL.	PAGE	
1889	I	227	Review. A Handbook of Therapeutics.
1891	II	1212	Article on Pulsations and Murmurs in the Great Veins of the Neck ; their Physiological and Clinical Significance. By Dr. Ringer and Dr. Harrington Sainsbury.
1891	II	1268	Ditto.
1892	I	740	Ditto.
1892	I	790	Ditto. Conclusion.
1894	I	325	Article on "Some Practical Points concerning the Diagnosis of Cardiac Murmurs." By Dr. Sydney Ringer and Dr. Arthur Phear.
1894	II	482	Review. A Handbook of Therapeutics.
1894	II	729	Article on "The Clinical Significance of Accentuated Second Sound." By Dr. Ringer and Dr. Arthur G. Phear.
1896	I	166	Clinical Society of London : Dr. Ringer and Dr. Arthur Phear contributed an Account of a Case of Addison's Disease treated with Suprarenal Extract.
1905	I	582	Reference to Dr. Ringer in a leading article on "Shifting Dullness in the Thorax and Abdomen."
1910	II	1386	Obituary Notice.

Papers and References in “The British Medical Journal.”

YEAR	VOL.	PAGE	
1859	—	680	Royal Medical and Chirurgical Society : An Abstract of a Paper by Dr. Ringer on “The Connection between the Heat of the Body and Excreted Amounts of Urea, Chloride of Sodium and the Urinary Water, during a Fit of Ague.”
1860	—	654	Royal Medical and Chirurgical Society : Paper by Dr. Ringer on “The Relative Amount of Sugar and Urea in the Urine of Diabetes Mellitus.” Communicated by Mr. Richard Quain, F.R.S.
1861	I	343	Note <i>re</i> a Paper by Dr. Ringer, in the Edinburgh Medical Journal of February, 1861.
1862	I	211	Royal Medical and Chirurgical Society : Paper by Dr. Ringer on “The Temperature, Urea, Chloride of Sodium and Urinary Water in Scarlet Fever and on a Cycle in Disease and Health.” Communicated by A. B. Garrod, M.D., F.R.S.
1865	I	248	Review. “On the Temperature of the Body as a Means of Diagnosis in Phthisis and Tuberculosis.” By Dr. Ringer.
1866	II	289	Royal Medical and Chirurgical Society : “The Influence of Alcohol on the Temperature of Non-Febrile and Febrile Persons. By Dr. Ringer and Walter Rickards, M.D.
1869	II	269	Review. “A Handbook of Therapeutics.” By Dr. Ringer.
1874	II	288	On the Action of Croton-Chloral Hydrate in Certain Forms of Megrin. (Abstract : Proceedings of Section of Medicine, Annual Meeting, British Medical Association, Norwich).
1874	II	637	Paper in full.
1875	I	380	On the Value of Tar in Bronchial Catarrh and Winter Cough. By Dr. Ringer and W. M. Murrell, L.R.C.P., M.R.C.S.

YEAR	VOL.	PAGE	
1875	I	543	"On Jaborandi."
1875	II	425	A Case of Rheumatic Hyperpyrexia cured by one Cold Bath.
1875	II	775	"A Case of Diabetes Insipidus treated by (1) Jaborandi and (2) Ergot."
1881	I	159	University College Hospital : "A Case of Delirium in Acute Rheumatism under the care of Dr. Ringer. Reported by Mr. David Collingwood.
1882	I	539	University College Hospital : "A Case of Epithelioma of Œsophagus under the care of Dr. Ringer." Reported by Mr. S. H. Collins.
1882	I	943	Royal Medical and Chirurgical Society : "The Action of Salts of Potash, Soda and Ammonia on the Frog's Heart." By Dr. Ringer and Dr. Harrington Sainsbury.
1882	II	1134	"Action of the Element Arsenic." By Dr. Ringer and Dr. Harrington Sainsbury.
1882	II	1193	Continued.
1883	I	451	"An Experimental Investigation of the Action of Chloral, Opium and Bromide of Potassium." By Dr. Ringer and Dr. Harrington Sainsbury.
1883	I	556	Continued.
1883	II	265	"Investigations into the Physiological Action of Barium Chloride." By Dr. Ringer and Dr. Harrington Sainsbury.
1883	II	925	Review. "A Handbook of Therapeutics." By Dr. Ringer.
1883	II	1070	Royal Medical and Chirurgical Society : "Investigations into the Action of the Digitalis Group."
1884	I	97	"Note on some Experiments with Ergotine." By Dr. Ringer and Dr. Harrington Sainsbury.
1884	II	114	Report on the Influence of Rhombic Sodium Phosphate and Sodium Bicarbonate on Muscular Contraction.
1885	I	731	Regarding the Effect of the Saline Ingredients of the Blood on the Contractions of the Heart.
1886	I	303	Review. "A Handbook of Therapeutics." By Dr. Ringer.

YEAR	VOL.	PAGE	
1887	II	1033	Address to the Midland Medical Society : "The Antagonism of Drugs."
1888	I	1257	"Remarks on Paroxysmal Sneezing." By Dr. Ringer and Dr. Murrell. Part I.
1888	I	1327	Part II.
1889	I	139	Review. "A Handbook of Therapeutics." By Dr. Ringer.
1894	II	1499	University College Hospital : Notes on the Antitoxin Treatment of Diphtheria, under the care of Dr. Ringer. Reported by Mr. F. Travers.
1895	II	1412	"Preparation of Milk for Diabetic Patients."
1895	II	1524	Letter by Dr. Ringer on "Preparation of Milk for Diabetic Patients."
1896	I	150	Clinical Society of London : "Addison's Disease treated with Suprarenal Extract." By Dr. Ringer and Dr. Arthur Phear.
1896	II	195	University College Hospital : Case of Antifebrin Poisoning, under the care of Dr. Ringer. Reported by Dr. Alfred Dimsey.
1896	II	1543	Letter by Dr. Ringer on "Belladonna in Bronchitis."
1898	I	701	Review. "A Handbook of Therapeutics." By Dr. Ringer.
1901	I	398	Royal Medical and Chirurgical Society : Remarks by Dr. Ringer during a discussion on "The Outbreaks of Arsenical Poisoning in Beer Drinkers."
1910	II	1276	Formal Note announcing the Death of Dr. Ringer.
1910	II	1384	Obituary Notice.



$$\begin{array}{r} 15 \\ \hline 10 \\ \hline 85 \end{array}$$

